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ANTIMICROBIAL RESISTANCE IN KLEBSIELLA PNEUMONIAE AT THE HUMAN–ANIMAL–ENVIRONMENT INTERFACE: A ONE HEALTH REVIEW

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Abstract

Klebsiella pneumoniae is an ubiquitous opportunistic pathogen, and has become a high priority pathogen on the World Health Organization (WHO) bacterial priority pathogens list, mainly because of the quick dissemination of multidrug-resistant (MDR) and hypervirulent strains all over the world. This review covers the epidemiology, transmission patterns and molecular mechanisms of antimicrobial resistance (AMR) in K. pneumoniae in humans, animals and the environment from a One Health perspective. We consolidate knowledge from genomic surveillance studies, showing that there is a significant overlap between human and non-human K. pneumoniae populations, and that high-risk sequence types like ST11 and ST258 are present in a variety of hosts. Hypervirulence in lineages such as ST23-KL57 is a growing threat to public health because it is now combined with resistance to the carbapenems. Mobile genetic elements such as plasmids are the main agents of horizontal transmission of resistance and virulence. Wastewater facilities and agriculture are important environmental reservoirs that facilitate the spread of AMR. We emphasize the advances in diagnostics, prevention and the critical importance of establishing genomic surveillance networks that support evidence-based response to this pathogen's complex threat.

1. INTRODUCTION

Antimicrobial resistance (AMR) is one of the greatest public health problems of the twenty first century. In 2019, an estimated five million deaths were linked to AMR, and if the rate of increase continues unabated, the number of deaths associated with AMR may reach 10 million a year by 2050. Klebsiella pneumoniae is one of the pathogens responsible for this crisis and is listed as a critical priority pathogen by the World Health Organization (WHO) for which there is an urgent need to develop new antimicrobial agents [1].

K. pneumoniae is a Gram-negative, encapsulated bacterium that is a member of the Enterobacteriaceae family and is widespread in the environment and is capable of colonizing a variety of hosts including humans, livestock, pets, wildlife, and the environment (soil, water). Its clinical importance is due to its status as a major cause of healthcare-associated infections such as pneumonia, bloodstream infections, urinary tract infections and meningitis, especially in immunocompromised patients [2]. This resistance ability to the organism through horizontal gene transfer has resulted in the emergence of multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) strains, which have reduced the options for treatment [3].

K. pneumoniae is a pathogen that has become a paradigm of One Health pathogen as it can be found in humans, animals and in the environment. Pathogen has been found in animals (including livestock, poultry, companion animals, wildlife and aquaculture fish), and there is genomic evidence of animal-to-human transmission and vice versa. Wastewater and agricultural systems are important environmental reservoirs for the spread of resistance genes. The recent emergence of hypervirulent K. pneumoniae (hvKp) strains that have a high virulence potential and are highly resistant to multiple antimicrobial agents highlights the need for multi-sectoral surveillance strategies [4].

The purpose of this review is to give a One Health perspective on AMR in K. pneumoniae. We review the biology and virulence determinants of the pathogen, its epidemiology in humans, wildlife and environmental reservoirs, the molecular mechanisms of resistance, and discuss the importance of diagnostic tools, prevention, and future research priorities needed to tackle this complex pathogen.

2. Biology and Pathogenicity of *Klebsiella pneumoniae*

2.1 Taxonomy and General Characteristics

K. pneumoniae is a member of the family Enterobacteriaceae, and is closely related to *K. quasipneumoniae* and *K. variicola*, which along with K. pneumoniae form the K. pneumoniae complex. It's a non-motile, facultatively anaerobic, lactose-fermenting gram-negative rod with a prominent polysaccharide capsule that results in the typical mucoid colony morphology. It has high genetic diversity with more than 500 sequence types (STs) found worldwide indicative of its ability to adapt to different ecological niches [5].

2.2 Virulence Factors

The virulence of K. pneumoniae is orchestrated by a suite of virulence determinants which allows colonization, evasion of immune response, and damage to tissues. The major virulence determinant is the capsular polysaccharide (CPS) which protects the bacterium from phagocytosis and complement-mediated killing. More than 160 capsular (K) serotypes have been identified with K1, K2, K5, K54, and K57 being associated with increased invasiveness. Capsule biosynthesis genes are located on the cps locus of the chromosome, and plasmidborne regulators like rmpA and rmpA2 are responsible for the appearance of hypermucoviscosity [6].

Lipopolysaccharide (LPS) has a role in serum resistance and in inflammatory responses. Lipid A anchors an O antigen molecule to the outer membrane of the cell, and also induces host inflammatory responses, and the O-antigen part protects against the deposition of complement. Fimbriae type 1 and type 3 pili are important for adhesion on mucosal surface and abiotic surface respectively leading to the formation of biofilm. The mrk gene cluster is of special significance for the formation of biofilm on medical devices, via the type 3 fimbriae. biofilm formation helps in persistent colonization and increases resistance to antibiotics and host immune response [7].

Siderophores are essential in the acquisition of iron in the iron restricted host environment. K. pneumoniae synthesizes several siderophores such as enterobactin (encoded by the chromosome), yersiniabactin (encoded by ICEKp), aerobactin and salmochelin (encoded by chromosomal genes located on plasmids). Hypervirulent phenotype is highly associated with the presence of aerobactin (iucABCD-iutA) and salmochelin (iroBCDN) genes [8].

Hypervirulent K. pneumoniae (hvKp) strains differ from classical strains by the presence of hypervirulence determinants. The aerobactin locus (iuc), which can be accompanied by iroBCDN and rmpA/rmpA2, is the genetic description of hvKp. These strains have been responsible for severe invasive infections such as liver abscesses, endophthalmitis, and meningitis in otherwise healthy persons. The pks genomic island, which also encodes the genotoxin colibactin, has been suggested to play a role in tissue virulence [9].

2.3 Clinical Manifestations

Nosocomial infections are mostly associated with classical K. pneumonia (cKp) in hospitalized patients with underlying comorbidities, such as pneumonia, urinary tract infections, bacteremia, and surgical site infections. Healthcare-associated infections include ventilator-associated pneumonia and catheter-associated urinary tract infections. Cep steady state pneumonia, especially in patients with chronic alcoholism or diabetes is a classic presentation of cKp infection [10].

Hypervirulent K. pneumoniae (hvKp) is characterized with its ability to induce characteristic clinical syndromes in the immunocompetent populations, such as pyogenic liver abscess, endophthalmitis, meningitis and necrotizing fasciitis. For the ST23-KL1 lineage, scatterings are particularly noted in East Asia where they are associated with community-acquired liver abscess. The CR-hvKp strains are seen to cause severe infections in the hospital and community with a mortality rate of more than 42% in some series [11].

2.4 High-Risk Clones and Hypervirulent Lineages

Multiple high risk clones have turned themselves into dominant disseminators of AMR. The most common MDR lineage worldwide is called ST11, and is linked to KL64 and KL47 capsular types, which are both found in Asia. Carbapenemase genes such as blaKPC-2, blaNDM-1 and blaOXA-48 are often found in ST11 strains. The ST11-KL64 CR-hvKp subclone showed that it had a marked growth potential, which probably depended on genetic components that gave them a survival advantage [12].

ST258 is a widely distributed lineage, mostly spread on a global level and is seen in both human and animal hosts, indicating that host barrier crossing is possible with this lineage, and is primarily reported to be carbapenem resistant with the ability to produce KPC. ST23 is the archetype of hvKp lineage, which is highly correlated with K1 capsular type and the hypervirulent phenotype. Dual carbapenemase strains (ST23-KL57) have been recently detected and are a worrisome combination of resistance and virulence [13].

3. The One Health Concept in Antimicrobial Resistance

3.1 Principles of One Health

The definition of the One Health approach means to see all aspects of human, animal and environmental health as interdependent and interwoven, so that the best health outcomes are achieved by working together in many sectors and in a multidisciplinary way. One Health recognizes that resistant organisms and genes do not observe conventional disciplinary lines, but rather move across complex discipline-hopping networks of human, animal, food production and environmental sectors in the context of AMR. The consequences for a paradigm change for surveillance, prevention, and control are enormous [14].

3.2 Why *K. pneumoniae* Fits the One Health Paradigm

K. pneumoniae exemplifies a One Health pathogen with the ability to move across multiple reservoirs, to show potential for cross species transmission and ability to act as a vector for spread of resistance and virulence determinants. There's been evidence of bidirectional transmission, as genomic analysis has shown no clear genetic boundaries among human- and animal-derived strains. Sectors must be overcome by unified sequence types, mobile genetic elements and resistance genes; siloed approaches are not sufficient [15].

3.3 Human–Animal–Environment Connectivity

K. pneumoniae transmission from humans to animals or vice versa, or from animals to the environment and then to humans, is complex. This pathogen has complex epidemiology and can spread by direct contact from colonised animals, by contaminated food products, via water and soil, and by health care facilities. Reverse zoonosis also comes in the picture, where man transfer the resistant sticks to animals [16].

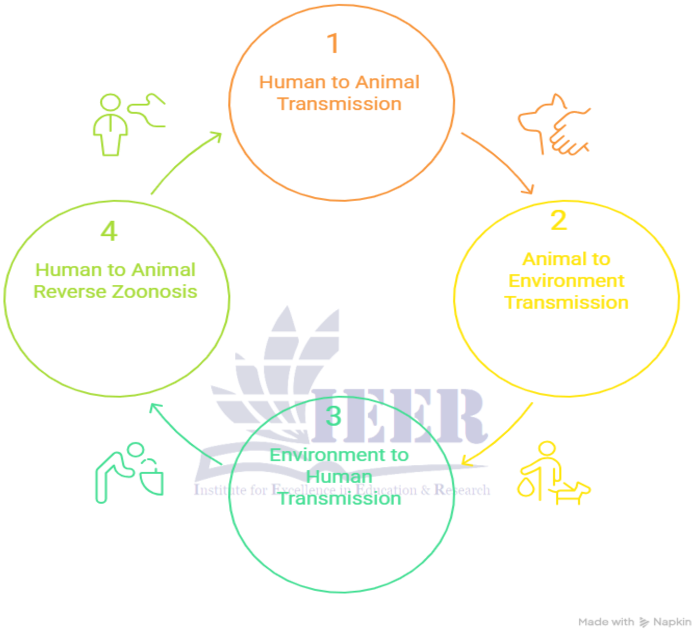

Figure 1.0 The transmission dynamics of K. pneumoniae: Human–Animal–Environment Connectivity

4. Epidemiology of Antimicrobial-Resistant *K. pneumoniae*

4.1 Global Burden

K. pneumoniae is one of the most common pathogens of nosocomial infections worldwide and is responsible for about 10% of nosocomial bacterial infections. CRKP is included on the 2024 WHO Bacterial Priority Pathogens List as the highest critical priority pathogen with the highest possible risk score (84%) among the 24 bacteria considered. This designation has been given to account for its disease burden, growing trend of resistance growing, treatment difficulty and significant impact to public health [17].

4.2 Regional Distribution

There are significant regional differences in the prevalence of AMR in K. pneumoniae. A systematic review and meta-analysis of ESBL-producing K. pneumoniae in sub-Saharan Africa reported a high prevalence of overall ESBL-producing K. pneumoniae, of which South Africa had highest prevalence (18.5%) and Central Africa had lowest prevalence (4.6%). The three countries with the highest numbers of ESBL-producing K. pneumoniae were South Africa (23.3%), Kenya (23%), and Nigeria (11.1%). High prevalence of MDR and ESBL-producing strains have been reported in Asia, in other countries ST11 and ST23 lineages prevail. High level spread of high-risk clones (especially ST258 with KPC production) has been observed in Europe and North America through surveillance networks [18].

4.3 Emerging High-Risk Sequence Types

In its way the world has been extensively documented with the dissemination of high-risk STs. ST11, ST258, ST15 and ST16 were the four most predominant K. pneumoniae types (16.1%, 8.3%, 6.4% and 4.1% respectively) with 57 countries represented. Of particular interest was the presence of ST11 in both human (16.1%) and non-human isolates (7.3%) with evidence of cross-sector transmission. Of particular concern is the recent development of ST23-KL57 strains that produce the two types of carbapenemases. ST23 strains were located in 42 countries, and 263 CR-hvKp ST23 strains (16.2%) in 22 countries were detected by analysing 1,622 ST23 genomes collected from 1980 to 2024. Genome of the newly emerged ST23-KL57 lineage (45 strains) showed higher level of antimicrobial resistance, lower genome sizes and absence of important chromosomal virulence loci, with 77.8% being CR-hvKp [19].

4.4 Hospital vs Community Epidemiology

K. pneumoniae traditionally is a hospital pathogen, but recently, community-acquired infections with hvKp have been reported in healthy individuals. With the emergence of strains of CR-hvKp with the potential to cause severe infection in both hospital and community settings, the boundaries of hospital and community epidemiology are becoming ill defined. Complications with stopping community transmission include the environmental and animal reservoirs [20].

5. Human Reservoirs and Transmission

Klebsiella spp. has a complex epidemiology in human population; the gastrointestinal tract of humans is considered as the usual source of human colonization, though asymptomatic colonization often induces clinical infections. K. pneumoniae is also known to be carried in the community from 5% to 38% of the community (stool carriage) and 1% to 6% of community members (nasopharangeal carriage); higher rates have been reported in the community in certain groups such as those of Chinese ethnicity; in these, carriage in stools has ranged from 19% in Japan to 88% in Malaysia. This significant difference highlights the role of host factors, geographical location and environmental exposures on the dynamics of colonization [21].

Health care environments are sensitive points of potential amplification of AMR K. pneumoniae. The proportion of colonized patients in the hospital environment is much higher, with up to 77 percent of stool samples and 19 percent of pharyngeal swabs and 42 percent of hand-drying samples being positive. The increase can be largely related to elimination of normal flora following antimicrobial therapy, allowing the successful establishment of resistant strains. The relevance of gastrointestinal colonization is highlighted by the fact that Klebsiella nosocomial infection is four times greater in stool carriers than in those who are not. In addition, use of ampicillin or amoxicillin within the last 30 days resulted in a higher risk for developing an infection in patients with K. pneumoniae liver abscesses [22].

The gastrointestinal tract provides a major reservoir for pathogen escape from the gastrointestinal tract, and establishment of colonization is a crucial intermediate step toward invasive infection. Systemic infection episodes have often been noted to be related to pre-existing colonization, especially in the high-risk intensive care units (ICU) and haematology wards (HW) through surveillance protocols that were established. In a six-month surveillance study, the rate of carbapenem-resistant K. pneumoniae (CRKP) colonization was 46.6%, and conversion into systemic infection was 4.9% of colonized cases, mostly in intensive care units (ICUs). This geographical change from colonization to infection underlines the need for active screening for asymptomatic colonization in high-risk groups [23].

An antifungal-resistant K. pneumoniae can spread from person to person via healthcare workers. Colonisation of the HCP is usually temporary but contaminated hands and equipment can spread resistant strains between patients. Persistent reservoirs may be seen in the healthcare setting such as surfaces, medical devices, and the water system. Rectal swabbing for CRE on admission and repeat in hospital could be considered as part of enhanced surveillance regimes to raise awareness and minimise negative effects of transmission [24].

The importance of travelers for spread of the antimicrobial-resistant K. pneumoniae strains has now been appreciated. People who visit countries where antimicrobial resistance is common could pick up resistant bacteria and bring them home, which helps spread antimicrobial resistance. Another route of community acquisition is foodborne transmission and K. pneumoniae has been found to be a foodborne pathogen from contaminated food products, such as hamburger meat. Clinically relevant lineages detected in ready-to-eat foods and vegetables highlight food supply chain as a transmission route [25].

6. Animal Reservoirs

6.1 Livestock and Poultry

Livestock and poultry production systems are large reservoirs of antimicrobial-resistant K. pneumoniae that can be spread to humans via direct contact, the food chain or the environment. Multidrug-resistant K. pneumonia in food animals is still a concern even though in some areas there are limits regulating the use of antimicrobial agents. In a study on prevalence of antibiotic-free poultry production systems, 29% of K. pneumoniae strains were identified as being antimicrobial resistant, 64% being multidrug resistant. The most prevalent multidrug-resistant combination protested five agents, both tetracycline and the other four drugs (ciprofloxacin, cefotaxime, gentamicin and trimethoprim/sulfamethoxazole). The observation of resistance that is independent of antimicrobial consumption, points to co-selection mechanisms and contamination of the environment [26].

The epidemiology of K. pneumoniae in livestock is significantly different among host species and production systems. Most strains of K. pneumoniae that have been isolated from cows with clinical mastitis in Australia were sensitive to all antimicrobial compounds tested and no 'superbug' (multidrug resistant) isolates were found. But in dairy cattle, the bacteria K. pneumoniae has been becoming more frequently associated with clinical mastitis with moderate to severe status, where therapeutic results are poor, resulting in high culling rates. The presence of STs known to be virulent in bovine diseases, such as ST65, in isolation from cases suggests improved surveillance is required for dairy farms [27].

6.2 Companion Animals

One factor of the One Health framework that has been underutilized is companion animals, such as dogs and cats. Companion animals live very near humans which aids the spread however surveillance has mainly concentrated on livestock and poultry. Surveillance also needs to incorporate companion animals since sequence types important in terms of clinical relevance have also been reported in canine and feline host [28].

6.3 Wildlife

Wildlife species act as sentinels and reservoirs of K. pneumoniae with antimicrobial resistance, which may be due to environmental contamination from humans and domesticated animals. Wild boar, fallow deer, roe deer, red deer, the European badger, magpie, red fox and wolf were sampled in a study of wild animals in Central Italy, with the result showing that 13% of these animals were positive for K. pneumonia. 56.2% of these wildlife isolates were notably multidrug resistant, with resistance to β-lactams, tetracycline, ertapenem, and trimethoprim. Genomic characterization revealed the genes responsible for fluoroquinolone resistance associated efflux pumps, fosfomycin and β-lactamase resistance genes, and virulence genes [29].

The emergence of clinically important resistance determinants in wildlife emphasises an ecological and epidemiological linkage between humans, wild animals and the natural environment. Resistant bacteria can be transmitted to wild animals via exposed environments such as farm seepage water, wastewater discharge and exposure to domestic animals. Detection of antimicrobial resistance genes in wildlife populations is a sign that human or livestock originated antimicrobial resistant bacteria are ubiquitous in the environment. The genetically related clustering of the wild boar isolates with available clinical genomes, indicated the strong possibility of wild boar-to-human transmission events [30].

Wild animals are efficient sentinels for the dissemination of antimicrobial resistance as they are likely to encounter environmental contamination, but not directly be under antimicrobial selection pressure. This trait makes it too important to monitor dissemination of resistant bacteria in the environment and evaluate how effective interventions are in minimizing environmental dissemination of resistant bacteria in wildlife [31].

6.4 Aquaculture

Several factors in aquaculture favor the spread of antimicrobial-resistant K. pneumoniae including the use of antimicrobials and discharge of waste water into aquatic environments. This commonshed water environment can enable resistance genes to transfer to other bacteria and ultimately to humans again via the ingestion of contaminated seafood. Mobile colistin resistance (mcr) genes have been identified in Klebsiella strains collected from chickens, pigs, silver gulls, hospital sewage effluent and wastewater treatment plants, respectively, which indicates interconnections between sectors. Plasmids from these sources harboured mcr variants which showed highly similar backbones indicating that transmission of colistin resistance can be seen in a One Health context [32].

7. Environmental Reservoirs

7.1 Wastewater as a Sentinel and Reservoir

Multimedia reservoirs and sentinel wastewater is an important source for information on antimicrobial-resistant K. pneumoniae human, animal and environmental reservoirs. Most antimicrobial resistant bacteria and resistance genes are contained in the effluent from wastewater treatment plants, which are coming from domestic and clinical source. Antibacterial resistance bacteria and genes are continuously discharged in the environment despite complying with the law recommendations of wastewater treatment [33].

K. pneumoniae has been detected throughout the world and even in Thailand, China, England and Japan in raw sewage in hospital wards. The presence of highly virulent K. pneumoniae in the wastewater is particularly alarming since such strains are found to have more abundance and range of virulence genes than do strains from other sources. Wastewater has the potential to be a larger reservoir of hypervirulent K. pneumoniae than the gut of people who are healthy, thus creating a serious public health threat [34].

Recent awareness of the potential risks posed to the environment from the release of large numbers of antimicrobial resistant bacteria and resistance genes into the environment has increased the importance of research to monitor antimicrobial resistance in wastewater treatment plants. Water quality and protection are crucial for social development and ecological sustainability due to the fact that the majority of water borne diseases, and antimicrobial resistant bacterial infections are transmitted through water [35].

7.2 Surface Water

We believe that via discharge of inadequately treated wastewater, agricultural return-flow and fecal contamination are the primary ways by which K. pneumoniae and other Enterobacteriaceae become surface water contaminants. Surface water studies have revealed a wide range of Klebsiella spp. species and sequence types (STs), of which the most common species is K. pneumoniae. Often, the profile of these isolates is extreme resistance to multiple drugs, and the prevalence of isolates that belong to sequence types (ST) as ST11, ST15 and ST147 among others indicates both animal and human origins [36].

The transfer of antibiotic resistance from naturally resistant environmental bacterial communities to non-resistant communities plays and critical role with regard to human, animal and ecosystem health. Mobile genetic elements (MGEs) contain genes that can confer antimicrobial resistance and potentially pathogenic bacteria shed into waters can harbor these genes that are integrated into

MGEs, which can spread among bacterial communities within the water body. Surface contamination by sewage, wastewater or hospital effluents, can cause the dispersion in the environment and the transmission to humans and animals by contact with water or even through wildlife [37].

7.3 Soil as a Reservoir

The soil is one of the largest and most diverse microbial habitats on Earth and also possesses perhaps the largest and most diverse population of microorganisms of all anthropogenic environments. Soil bacteria harbor antimicrobial resistance genes that can also be found in human clinical pathogens and in emerging pathogens yet to be discovered. Soil application of faecal material, especially in farming is a basic human activity that creates concern for the presence of antimicrobial resistance. Organic amendments are animal origin (manure) or human origin (biosolids) as valuable sources of nutrients for agricultural production, and are widely utilized for soil improvement. Irrigation with reclaimed wastewater may also harbor residues of pharmaceuticals like antibiotics as well as antimicrobial resistant bacteria depending on the method of treatment and is another practice that is becoming increasingly of concern [38].

Antibiotics residues in soil may cause variations between the preceding microorganisms, where bacteria resistance may dominate, and may be transferred to other ecological niches. Bacteriophages are reported to transfer more extensively, and faster, antimicrobial resistance genes in fertilized soil under antibiotic presence than under the absence of antibiotics. Antibiotics can also be selectively available for bacteria due to soil mineral and organic compounds [39].

7.4 Agricultural Environments

Agro-environmental facilities, such as farms, slaughterhouses and food processing plants are significant sites of dissemination of AR K. pneumoniae. ESBL-producing K. pneumoniae with clinically relevant resistance genes have been found in floor drainage and wastewater samples from abattoirs. Agricultural inputs help to contaminate the environment with resistant bacteria and genes to resistance in surface water and soil [40].

In the field of agriculture and livestock farming, antibiotics are everywhere, and have been identified as a possible driver toward the emergence of antibiotic-resistance in human health care. Presence of antimicrobial resistant K.pneumoniae in food chain has been reported with significant proportion in China, South Africa, Europe, Greece and Iran. This indicates that a considerable proportion of strains present in the food supply possess genetic characteristics of pathogenicity and resistance and are associated with a high survival potential in case of disease [41].

8. Food Chain Transmission

There is a significant transmission route from animal reservoirs to people via the food chain for transferring antimicrobial resistant K. pneumoniae. This has shown a previously unknown ecological niche of K. pneumoniae as an enteroinvasive foodborne pathogen from contaminated hamburger. This is a common food contaminant and is found in both animal- and plant-based food and diets and seems to be a major contributor to the exposure of environmental strains to the Human GUT [42].

8.1 Meat and Poultry Products

Antimicrobial-resistant K. pneumoniae may be transmitted to humans in food via food-producing animals, especially in meat products such as poultry and pork. The contamination is due to faecal shedding at slaughter, processing and handling. Multidrug resistant and ESBL-producing strains have been found in retail meat products worldwide, which may be a potential mode of exposure. The presence of sequence types (STs) that emerged from virulent turkey (ST25) and bovine (ST65) diseases in raw retail turkeys indicates the possibility of foodborne acquisition of clinically relevant STs [43].

8.2 Milk and Dairy Products

High levels of K. pneumoniae may be found in the milk of cows affected by illness due to mastitis.

Antimicrobial resistant strains may be harbored within unpasteurized milk, which offers a potential source of exposure, but not pasteurized milk. The ESBL-producing K. pneumoniae have been detected in mastitis milk, thereby stressing the importance of farm to fork surveillance [44].

8.3 Fresh Produce

K. pneumoniae is able to contaminate fresh produce via irrigation, manure, or colonized people. K. pneumonia lineages of clinical relevance are especially concerning having been present in ready to eat vegetables. A food supply chain mechanism of transmission may include the consumption of raw or minimally processed foods that may be exposed to antimicrobial-resistant strains. The presence of clinically important variants that were not of human origin and the high degree of similarity between patient and retail meat isolates based on whole genome sequencing are all supportive of the notion of foodborne transmission [45].

9. Molecular Mechanisms of Antimicrobial Resistance

9.1 β-Lactam Resistance

Production of β-lactamases that hydrolyse the β-lactam ring is the major mechanism of resistance to β-lactam antibiotics in K. pneumoniae. Extended-spectrum β-lactamases (ESBLs) such as TEM, SHV and CTX-M variants, is responsible for resistance to penicillin, cephalosporins and aztreonam antibiotics. In almost half of the K. pneumoniae sequences sensitive to carbapenems, the presence of more than one ESBL gene (CTX-M, SHV, TEM) has been identified. The most frequently reported ESBL gene worldwide is CTX-M-15, found in most of the isolates harboring carbapenemase genes [46].

9.2 Carbapenem Resistance

The most clinically significant resistance phenotype is carbapenem resistance, considerably reducing treatment options. The carbapenemases involve in this category include KPC (class A), NDM, VIM and IMP (class B metallo-β-lactamases) and OXA (class D). Invasive CRE-K.p. isolates were analysed, the overall incidence of carbapenemases was 87%, with the KPC-type in 57%, the OXA-type in 28%, and NDM-type in 16%. Most (87%) of the carrying carbapenemases were in conjugative or mobilizable plasmids, suggesting the possibility of being transferable to other strains [47].

The emergence of carbapenem-resistant hypervirulent *K. pneumoniae* (CR-hvKp) represents a convergence of resistance and virulence. The WHO has designated carbapenem-resistant *K. pneumoniae* as the top "critical priority" pathogen, assigning it the highest possible risk score (84%) among 24 evaluated bacteria. Patients with carbapenemase-producing CRKp strains have demonstrated increased in-hospital mortality compared to those with non-carbapenemase-producing strains [48].

9.3 Non-Carbapenemase Mechanisms

In the absence of enzymes (carbapenemase), the combination of ESBL enzymes and loss of porins can contribute to resistance to carbapenems. Of a total of 93 carbapenem-resistant isolates lacking detectable carbapenemases, 88% had mutations in the porin genes ompK35 and/or ompK36. 25% of these isolates contained a truncated versions of both ompK35 and ompK36 and 56% contained a inactivated version of ompK36 only. Mutations in porins were far from being numerous in carbapenemase-producing isolates (39%), implying that the selective pressure for porin loss is reduced when carbapenemases are produced [49].

9.4 Colistin Resistance

Colistin (polymyxin) is a polymyxin antibiotic that is a last line of defence against carbapenem resistance. The plasmid-mediated colistin resistance (mcr) genes have been found in Klebsiella samples from a variety of sources such as humans, chickens, pigs, silver gulls, hospital sewage, and wastewater treatment plants. Four incompatibility groups, the IncFII, IncHI2, IncI2, and IncX4, have been found in mcr variants by plasmid typing as the most commonly found. The high similarity of the plasmid backbones of all genomes between different hosts suggests that the spread of colistin resistance genes can also be studied in a One Health context, which is very likely to be from waste and food producing animals, but not necessarily under the pressure from antimicrobials in clinical settings [50].

9.5 Efflux Pumps and Porin Mutations

The efflux pumps are very important in intrinsic and acquired resistance. AcrAB-TolC is a multidrug efflux pump that is overexpressed to develop resistance to many classes of antibiotics. The most common predicted mechanism for carbapenem resistant isolates among the non-carbapenemase producers in the sense that they have been shown to produce ESBL, is ESBL production plus truncation of the porins. Insertional mutations within the porins decrease the uptake of the antibiotics, which is how high-level resistance to the β-lactam antibiotics is developed [51].

9.6 Mobile Colistin Resistance (mcr) Genes

All 10 mcr homologs were screened for over five years in a broad One Health study involving 2,855 clinical Klebsiella genomes, yielding 20 (0.7%) positive genomes (six different variants: mcr-1.1, mcr-8.1, mcr-8.2, mcr-9.1, mcr-9.2 and mcr-10.1). Inter-species and inter-patient transmission events were identified by plasmid analysis, which revealed the presence of mcr-containing plasmids on the chromosome of one of the ICRs, K. pneumoniae ST147, and in K. georgiana and E. coli [52].

10. Mobile Genetic Elements Driving Resistance

10.1 Plasmids

Plasmids are the most important means for horizontal transfer of antibiotic resistant and virulence determinants in K. pneumoniae. Conjugative plasmids have genes that allow them to be transferred and often contain several resistance genes that allow co-selection. Most carbapenemases (80%) are plasmid-encoded (conjugative plasmids), and 11% are located on mobilizable plasmids, suggesting that they are potentially transmissible. K. pneumoniae genes associated with the accessory genome are more likely to be mobilome-associated genes (14.6% vs 0.1% in the core genome), and the pathogen has been characterized as being highly plastic in its genome [53].

Recent findings demonstrate that mobile genetic elements have sophisticated mechanisms of dissemination, such as dissemination of conjugative virulence plasmids between bacteria, integrative conjugative element (ICE)-mediated transfer of virulence traits and hybrid genetic elements that provide both virulence and antimicrobial resistance [54].

10.2 Integrons and Transposons

Integrons are genetic units that capture and express blocks of genes in the form of gene cassettes that can confer resistance determinants by site-specific recombination. The antimicrobial resistance genes most commonly linked to class 1 integrons are found in K. pneumoniae, and may contain multiple resistance genes. Transposons contain resistance genes and can enable the transfer of genes of resistance to plasmids and other mobile elements. The plasmid helps to spread the blaKPC containing gene in trans, via a Tn3 transposon, Tn4401 [55].

10.3 Insertion Sequences

The ability of the small mobile element, known as insertion sequences (IS), to cause genetic diversity by making insertions, deletions and re-arrangements. IS elements can be seen to have a role in activation or inaction expression of genes and they have been reported to involve in the mobilization expression of resistance genes. The ISEcp1 element has been related to the spread of CTX-M ESBL genes [56].

10.4 Integrative Conjugative Elements

Integrative conjugative elements (ICEs) can integrate into the chromosome and excise and then transfer horizontally. ICEKp elements have been shown to be linked with the spread of genes coding for yersiniabactin and other virulence factors. These elements play a role in the evolution of hypervirulence in K. pneumoniae [57].

10.5 Horizontal Gene Transfer

The most important mechanism of dissemination of antimicrobial resistance is horizontal gene transfer in K. pneumoniae. The mobilization of resistance genes and virulence genes between bacterial populations and species is facilitated by plasmids, transposons and other mobile elements. Co-occurrence of multiple resistance determinants on the same mobile elements could induce co-selection and the formation of multi-resistance strain. Plasmid-mediated transmission has been proven to play a major role in recurrent CRKP infections with either the identical genomic group or the identical carbapenemase-encoding conjugative plasmids in different K. pneumoniae strains being responsible for the nosocomial transmission [58].

11. Genomic Epidemiology and Surveillance

11.1 Whole Genome Sequencing

Whole genome sequencing (WGS) has revolutionized the surveillance and characterization of AMR K. pneumoniae. WGS data offers complete insights into the resistome, virulome, plasmidome and phylogenetic affiliations of bacterial isolates, which allows comprehensive tracking of transmission chains with a high level of resolution and outbreak investigation [59].

11.2 MLST

Today, multi-locus sequence typing (MLST) is the most common method of subtyping K. pneumoniae populations and of discriminating "high-risk" clones. Comparisons and monitoring of epidemic lineages on a global scale are possible with the extensive MLST database. In the world, more than 500 STs have been detected, and the most important high-risk STs are ST11, ST258 and ST23 [60].

11.3 Resistome

The resistome is the copy of genes of antimicrobial resistance in the genome of a bacterium. Analysis of resistance helps to give a complete picture of the resistance profile of isolates and can highlight novel or emerging resistance determinants. Widespread prevalence of ESBL and carbapenemase genes in clinical and non-clinical organisms have been described well [5].

11.4 Virulome

The virulome encompasses all virulence genes present in a bacterial genome. Virulome analysis identifies hypervirulent lineages and tracks the evolution of virulence. The presence of aerobactin (*iuc*), salmochelin (*iro*), and *rmpA/rmpA2* genes distinguishes hvKp from classical strains[61].

11.5 Plasmidome

The plasmidome is the sum of a bacterial genome's plasmids. Plasmidome profiling can unmask distribution and dissemination of resistance and virulence determinants on mobile genetic elements. Particularly of concern are the resistance determinants which are found on conjugative plasmids and may be disseminated horizontally [62].

12.Human–Animal–Environment Transmission Pathways

12.1 Direct Contact

Close contact with animals that are colonised, especially with livestock and companion animals, may be a potential route of spread for AMR K. pneumoniae. Evidence for cross species transmission is strengthened by the absence of definite genetic boundaries between human and animal derived strains. A study of cell adhesion and invasion showed that K. pneumoniae strains isolated from different host species were not host-specific and this was in line with the idea of the potential for cross-species infection [63].

12.2 Foodborne Transmission

Foodborne transmission is via contaminated animal produce and/or produce. AMR K. pneumoniae has been found in meat, milk, as well as fresh produce, all over the world. The food chain is an important position where the genes of resistance can change from animal reservoirs to human populations [64].

12.3 Waterborne Transmission

Water-borne transmission is the result of exposure to contaminated surface water, ground water or poorly hydrated waste water. AMR K. pneumoniae is known to be present in environmental water and water borne exposure may occur, accentuating the importance of water quality management in preventing AMR K. pneumoniae transmission [65].

12.4 Environmental Dissemination

Environmental dissemination is done by resistance genes and resistant bacteria being released to the environment. Manure or agricultural run-off and discharge of waste water cause contamination. Resistance genes can be transferred horizontally to other bacteria once in the environment [66].

12.5 Reverse Zoonosis

When zoonotic pathogens are transferred to animals from humans this is reversible zoonosis or anthroponosis. Clones have been detected in animal populations, associated with humans, indicating reverse zoonosis can play a role in the epidemiology of AMR K. pneumoniae. Resistant strains can be spread to animals by healthcare workers, farmers and owners of animals [67].

Antimicrobial-resistant Klebsiella pneumoniae spreads through diverse interconnected human, animal, and environmental transmission routes.

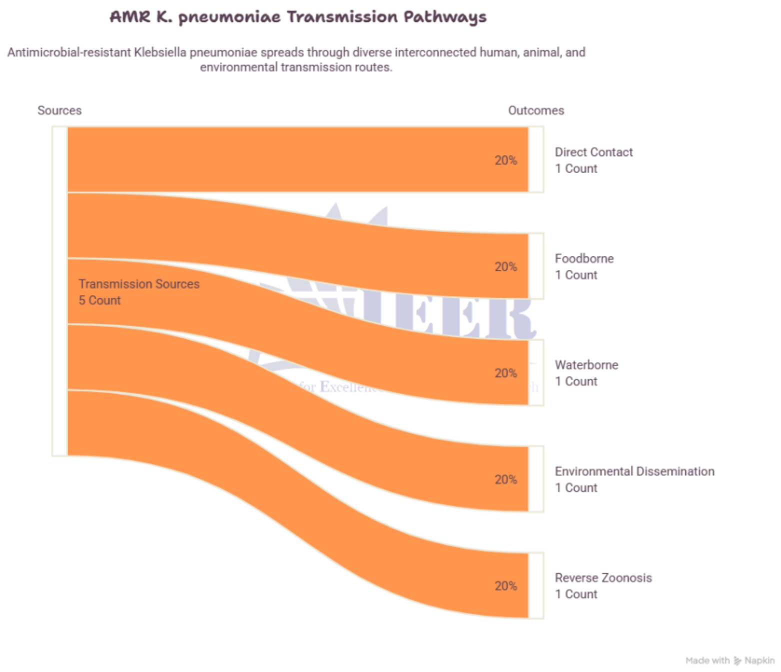

Figure 1.1

13. Diagnostic and Surveillance Approaches

13.1 Conventional Culture

The traditional method for identification of K. pneumoniae is still the gold standard procedure. Isolation and identification will be achieved using selective and differential media, e.g MacConkey agar and CHROMagar. Culture-based methods are important to isolate and characterize them and evaluate their antimicrobial susceptibility. Recurrent screening within the hospital for enterobacterales and other gram-negative bacteria that may be carbapenem resistant is recommended using rectal swabs for active surveillance patient admission and periodically [24].

13.2 Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing (AST) is used to find the antibiotic resistance status of the isolated strains. The disc diffusion, broth microdilution, and gradient strip methods are all used commonly. The EUCAST guidelines are used to interpret the minimum inhibitory concentration (MIC) results for guiding clinical management and for informing the surveillance. The BD Phoenix system has been cleared for use in surveillance testing for identification and antimicrobial susceptibility testing [68].

13.3 PCR-Based Detection

Polymerase chain reaction (PCR)-based methods are available for the detection of specific resistance or virulence genes, and these offer a rapid method of identifying target determinants. Multiple genes can be detected in a multiplex PCR assay, thus optimizing the procedure. There are PCR techniques available for screening of ESBL gene and Carbapenemase gene. The GeneXpert Carba-R cartridges have been used to confirm the presence of carbapenemase genes in surveillance programme [69].

14. Prevention and Control Strategies

14.1 Antimicrobial Stewardship

The goal of ASPs is to improve antibiotic prescribing practices to minimize selective pressure. Elements include suitable prescribing, de-escalation of therapy and review of antimicrobials. Stewardship strategies have proven to be successful at lowering AMR rates among health-care settings [70].

14.2 Infection Prevention

IP and C measures play an important role in minimizing the spread of AMR K. pneumoniae in healthcare facilities. These include maintaining good hand hygiene, contact precautions, cleaning the environment, and actively monitoring for carriage. One Health-related innovative infection prevention activities are encouraged to slow the spread of K. pneumoniae [71].

14.3 Veterinary Stewardship

Veterinary stewardship efforts focus on minimizing antimicrobial use in the production of food animals and through veterinarians as part of pet care. Educating the surrounding of the necessity of reducing use of a highly valuable antimicrobial in animals and encouraging monitoring programs are key steps. Veterinary stewardship helps to remove selection pressure and decrease the spread of resistant strains [72].

14.4 Environmental Management

The objective of environmental management strategies is to minimize pollution to the environment with AMR bacteria and resistance genes. The proper management of wastes, treatment of water in the agriculture, treatment of hospital water and cleaning of environmental surfaces are important parts of it [73].

14.5 Wastewater Treatment

The pollution control treatment of wastewater is critical to minimise effluent discharge of AMR bacteria and AMR genes to the environment. New treatment technologies can drastically minimize the levels of resistances in treated effluents. Wastewater surveillance should be part of wastewater treatment monitoring [74].

14.6 Vaccines

Vaccines are a potential method to prevent K. pneumoniae infections and to reduce antibiotic use. Capsular polysaccharides, O-antigens and protein antigens have been focus of the vaccine development. There is a potential to significantly impact disease burden with vaccines for high-risk individuals such as hospitalized patients and livestock [75].

14.7 Phage Therapy

Phage therapy is a new type of treatment for AMR infections. Phages further have a very specific target, such as K. pneumoniae, and do not harm the normal flora. Although phage cocktails and engineered phages may show promise compared to conventional antibiotics, phage resistance is also a worry [76].

14.8 CRISPR-Based Antimicrobials

In the field of antimicrobials, CRISPR based antimicrobials exploit CRISPR-Cas system to target specific resistance or virulence genes in bacteria. This strategy has a strong specificity and potentially could be used to eliminate the MDR K. pneumoniae strain with not affecting on the susceptible bacteria [77].

Conclusions

K. pneumoniae is a model organism of the complex epidemiology of AMR at the human–animal–environment nexus. The invasive nature of the pathogen, ability to infect multiple species, and potential to carry resistance and virulence factors emphasize limitations of “silo mentality” surveillance and control measures. High-risk clones are found on human and non-human hosts, and the appearance of strains of CR-hvKp are especially worrying. Carbapenem resistance and hypervirulence of Carbapenem resistant-hypervirulent klebsiella (CRKK) in an ascending order of alluded lineages such as ST23-KL57 are a call for heightening the vigilance and coordinated intervention strategies. The rapid evolution and dissemination of high-risk clones is mainly due to horizontal transfer of resistance and virulence determinants, which occurs because of genetic elements that move among cells, including plasmids. The various environmental reservoirs, such as wastewater and agricultural environment, are key points in the transmission network.

To combat the risk of AMR K. pneumoniae, an integrated clinical, veterinary and environmental surveillance program is needed. High resolution genome sequence data from genomic surveillance, such as WGS and metagenomics, is key to tracing transmission routes, detecting new threats and opportunities. WWE is a resource-saving system for monitoring populations. An antimicrobial stewardship program, infection prevention program, and a veterinary stewardship program are all critical elements of a comprehensive control strategy. Looking forward, there is a need to focus on increasing surveillance capacity in LMICs, bring the various sectoral genomics databases together, and create standardised reporting systems. Antimicrobial resistance from MDR and XDR bacteria is a field with high nutrient value inputs that are being researched, seeking other methods of therapy such as vaccine, phage and antimicrobials using Crispr–Cas9 system. Finally, a One Health approach to tackle this threat and safeguard global health that works with multiple disciplines, including collaboration between human and animal health, and the environment is necessary.

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REFERENCES

[1] A. B. Janssen *et al.* , “Klebsiella pneumoniae OmpR facilitates lung infection through transcriptional regulation of key virulence factors,” *IRIS* , vol. 12, no. 1, Dec. 2023, doi: 10.1128/spectrum.03966-23.

[2] F. C. Morris, C. Dexter, X. Kostoulias, M. I. Uddin, and A. Y. Peleg, “The Mechanisms of Disease Caused by Acinetobacter baumannii,” *Frontiers in Microbiology* , vol. 10, pp. 1601–1601, Jul. 2019, doi: 10.3389/fmicb.2019.01601.

[3] M. C. Arendrup and T. F. Patterson, “Multidrug-Resistant Candida: Epidemiology, Molecular Mechanisms, and Treatment,” *The Journal of Infectious Diseases* , vol. 216, Mar. 2017, doi: 10.1093/infdis/jix131.

[4] M. Lee, N. Kuan, Z. Li, and K. Yeh, “Occurrence and characteristics of extended-spectrum-β-lactamase- and pAmpC-producing Klebsiella pneumoniae isolated from companion animals with urinary tract infections,” *PLoS ONE* , vol. 19, no. 1, Jan. 2024, doi: 10.1371/journal.pone.0296709.

[5] M. M. C. Lam, R. R. Wick, S. C. Watts, L. Cerdeira, K. L. Wyres, and K. E. Holt, “A genomic surveillance framework and genotyping tool for Klebsiella pneumoniae and its related species complex,” *Nature Communications* , vol. 12, no. 1, pp. 4188–4188, Jul. 2021, doi: 10.1038/s41467-021-24448-3.

[6] J. Zhu, T. Wang, L. Chen, and H. Du, “Virulence Factors in Hypervirulent Klebsiella pneumoniae,” *Frontiers in Microbiology* , vol. 12, pp. 642484–642484, Apr. 2021, doi: 10.3389/fmicb.2021.642484.

[7] L. Li *et al.* , "Relationship between biofilm formation and antibiotic resistance of Klebsiella pneumoniae and updates on antibiofilm therapeutic strategies," *Frontiers in Cellular and Infection Microbiology* , vol. 14, pp. 1324895–1324895, Feb. 2024, doi: 10.3389/fcimb.2024.1324895.

[8] T. A. Russo *et al.* , "Aerobactin Mediates Virulence and Accounts for Increased Siderophore Production under Iron-Limiting Conditions by Hypervirulent (Hypermucoviscous) Klebsiella pneumoniae," *Infection and Immunity* , vol. 82, no. 6, pp. 2356–2367, Mar. 2014, doi: 10.1128/iai.01667-13.

[9] J. R. Johnson, B. Johnston, M. A. Kuskowski, J. Nougayrède, and E. Oswald, "Molecular Epidemiology and Phylogenetic Distribution of the Escherichia coli pks Genomic Island," *Journal of Clinical Microbiology* , vol. 46, no. 12, pp. 3906–3911, Oct. 2008, doi: 10.1128/jcm.00949-08.

[10] S. Lepuschitz *et al.* , "Fecal Klebsiella pneumoniae Carriage Is Intermittent and of High Clonal Diversity," *Frontiers in Microbiology* , vol. 11, pp. 581081–581081, Nov. 2020, doi: 10.3389/fmicb.2020.581081.

[11] C. Struve *et al.* , "Mapping the Evolution of Hypervirulent Klebsiella pneumoniae," *mBio* , vol. 6, no. 4, Jul. 2015, doi: 10.1128/mbio.00630-15.

[12] T. Chen *et al.* , "Recombination Drives Evolution of Carbapenem-Resistant Klebsiella pneumoniae Sequence Type 11 KL47 to KL64 in China," *PubMed Central* , vol. 11, no. 1, Jan. 2023, doi: 10.1128/spectrum.01107-22.

[13] C. Shankar *et al.* , "Emergence of Multidrug Resistant Hypervirulent ST23 Klebsiella pneumoniae: Multidrug Resistant Plasmid Acquisition Drives Evolution," *Frontiers in Cellular and Infection Microbiology* , vol. 10, pp. 575289–575289, Nov. 2020, doi: 10.3389/fcimb.2020.575289.

[14] K. E. Arnold *et al.* , "The need for One Health systems-thinking approaches to understand multiscale dissemination of antimicrobial resistance," *The Lancet Planetary Health* , vol. 8, no. 2, Feb. 2024, doi: 10.1016/s2542-5196(23)00278-4.

15] M. Struelens, C. Ludden, G. Werner, V. Sintchenko, P. Jokelainen, and M. Ip, "Real-time genomic surveillance for enhanced control of infectious diseases and antimicrobial resistance," *Frontiers in Science* , vol. 2, Apr. 2024, doi: 10.3389/fsci.2024.1298248.

[16] L. Boden and D. J. Mellor, "Epidemiology and Ethics of Antimicrobial Resistance in Animals," in *Public health ethics analysis* , Springer Nature (Netherlands), 2020, pp. 109–121. doi: 10.1007/978-3-030-27874-8_7.

[17] T. Jesudason, "WHO publishes updated list of bacterial priority pathogens," *The Lancet Microbe* , vol. 5, no. 9, pp. 100940–100940, Jul. 2024, doi: 10.1016/j.lanmic.2024.07.003.

[18] C.-R. Lee, J. H. Lee, K. S. Park, Y. B. Kim, B. C. Jeong, and S. H. Lee, "Global Dissemination of Carbapenemase-Producing Klebsiella pneumoniae: Epidemiology, Genetic Context, Treatment Options, and Detection Methods," *Frontiers in Microbiology* , vol. 7, pp. 895–895, Jun. 2016, doi: 10.3389/fmicb.2016.00895.

[19] T. Chen, X. Wang, L. Xiong, P. Shen, and Y. Xiao, "Emergence and molecular evolution of carbapenem-resistant hypervirulent ST23 Klebsiella pneumoniae : The superbug phenomenon in China," *Virulence* , vol. 16, no. 1, pp. 2545556–2545556, Aug. 2025, doi: 10.1080/21505594.2025.2545556.

[20] A. Spadar, J. Perdigão, S. Campino, and T. G. Clark, "Large-scale genomic analysis of global Klebsiella pneumoniae plasmids reveals multiple simultaneous clusters of carbapenem-resistant hypervirulent strains," *Genome Medicine* , vol. 15, no. 1, pp. 3–3, Jan. 2023, doi: 10.1186/s13073-023-01153-y.

[21] K. Goh, W. Chan, S. Shiota, and Y. Yamaoka, "Epidemiology of Helicobacter pylori Infection and Public Health Implications," *Helicobacter* , vol. 16, pp. 1–9, Sep. 2011, doi: 10.1111/j.1523-5378.2011.00874.x.

[22] Y.-T. Lin, C. Liu, Y. Yeh, T. Chen, and C.-P. Fung, "Ampicillin and Amoxicillin Use and the Risk of Klebsiella pneumoniae Liver Abscess in Taiwan," *The Journal of Infectious Diseases* , vol. 208, no. 2, pp. 211–217, Apr. 2013, doi: 10.1093/infdis/jit157.

[23] F. Briano *et al.* , "Candida auris Candidemia in Critically Ill, Colonized Patients: Cumulative Incidence and Risk Factors," *Infectious Diseases and Therapy* , vol. 11, no. 3, pp. 1149–1160, Apr. 2022, doi: 10.1007/s40121-022-00625-9.

[24] A. Guh, B. Limbago, and A. J. Kallen, "Epidemiology and prevention of carbapenem-resistant Enterobacteriaceae in the United States," *Expert Review of Anti-infective Therapy* , vol. 12, no. 5, pp. 565–580, Mar. 2014, doi: 10.1586/14787210.2014.902306.

[25] C. L. Gorrie *et al.* , "Genomic dissection of the bacterial population underlying Klebsiella pneumoniae infections in hospital patients: insights into an opportunistic pathogen," Dec. 09, 2021. doi: 10.1101/2021.12.02.21267161.

[26] L. Murray, A. Hayes, J. Snape, B. Kasprzyk-Hordern, W. H. Gaze, and A. K. Murray, "Co-selection for antibiotic resistance by environmental contaminants," *npj Antimicrobials and Resistance* , vol. 2, no. 1, pp. 9–9, Apr. 2024, doi: 10.1038/s44259-024-00026-7.

[27] R. A. Rodrigues *et al.* , "Comparative genomics study of Staphylococcus aureus isolated from cattle and humans reveals virulence patterns exclusively associated with bovine clinical mastitis strains," *Frontiers in Microbiology* , vol. 13, pp. 1033675–1033675, Nov. 2022, doi: 10.3389/fmicb.2022.1033675.

[28] S. Abraham, H. S. Wong, J. Turnidge, J. R. Johnson, and D. J. Trott, "Carbapenemase-producing bacteria in companion animals: a public health concern on the horizon," *Journal of Antimicrobial Chemotherapy* , vol. 69, no. 5, pp. 1155–1157, Jan. 2014, doi: 10.1093/jac/dkt518.

[29] B. Awosile *et al.* , "Genomic Characterization of Fecal Escherichia coli Isolates with Reduced Susceptibility to Beta-Lactam Antimicrobials from Wild Hogs and Coyotes," *Pathogens* , vol. 12, no. 7, pp. 929–929, Jul. 2023, doi: 10.3390/pathogens12070929.

[30] A. Mercato *et al.* , "Wild Boars as an Indicator of Environmental Spread of ESβL-Producing Escherichia coli," *Frontiers in Microbiology* , vol. 13, pp. 838383–838383, Apr. 2022, doi: 10.3389/fmicb.2022.838383.

[31] C. Doyle, K. Wall, S. Fanning, and B. J. McMahon, "Making sense of sentinels: wildlife as the One Health bridge for environmental antimicrobial resistance surveillance," *Journal of Applied Microbiology* , vol. 136, no. 1, Jan. 2025, doi: 10.1093/jambio/lxaf017.

[32] S. D. Koster *et al.* , "One Health surveillance of colistin-resistant Enterobacterales in Belgium and the Netherlands between 2017 and 2019," *PLoS ONE* , vol. 19, no. 2, Feb. 2024, doi: 10.1371/journal.pone.0298096.

[33] S. Fletcher, "Understanding the contribution of environmental factors in the spread of antimicrobial resistance," *Environmental Health and Preventive Medicine* , vol. 20, no. 4, pp. 243–252, Apr. 2015, doi: 10.1007/s12199-015-0468-0.

[34] L. Măruțescu *et al.* , "Wastewater treatment plants, an 'escape gate' for ESCAPE pathogens," *Frontiers in Microbiology* , vol. 14, pp. 1193907–1193907, May 2023, doi: 10.3389/fmicb.2023.1193907.

[35] F. Cutrupi *et al.* , "Towards monitoring the invisible threat: a global approach for tackling AMR in water resources and environment," *Frontiers in Water* , vol. 6, Mar. 2024, doi: 10.3389/frwa.2024.1362701.

[36] L. Falgenhauer *et al.* , "Multidrug-Resistant and Clinically Relevant Gram-Negative Bacteria Are Present in German Surface Waters," *Frontiers in Microbiology* , vol. 10, pp. 2779–2779, Nov. 2019, doi: 10.3389/fmicb.2019.02779.

[37] M. Uyaguari *et al.* , "Human Activity Determines the Presence of Integron-Associated and Antibiotic Resistance Genes in Southwestern British Columbia," *Frontiers in Microbiology* , vol. 9, pp. 852–852, May 2018, doi: 10.3389/fmicb.2018.00852.

[38] P. Hong, N. Al-Jassim, M. I. Ansari, and R. I. Mackie, "Environmental and Public Health Implications of Water Reuse: Antibiotics, Antibiotic Resistant Bacteria, and Antibiotic Resistance Genes," *Antibiotics* , vol. 2, no. 3, pp. 367–399, Jul. 2013, doi: 10.3390/antibiotics2030367.

[39] A. C. Singer, H. M. Shaw, V. Rhodes, and A. Hart, "Review of Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators," *Frontiers in Microbiology* , vol. 7, pp. 1728–1728, Nov. 2016, doi: 10.3389/fmicb.2016.01728.

[40] S. Araújo, V. Silva, M. Quintelas, Â. Martins, G. Igrejas, and P. Poeta, "From soil to surface water: exploring Klebsiella 's clonal lineages and antibiotic resistance odyssey in environmental health," *BMC Microbiology* , vol. 25, no. 1, pp. 97–97, Feb. 2025, doi: 10.1186/s12866-025-03798-8.

[41] L. L. Founou, R. C. Founou, and S. Y. Essack, "Antibiotic Resistance in the Food Chain: A Developing Country-Perspective," *Frontiers in Microbiology* , vol. 7, pp. 1881–1881, Nov. 2016, doi: 10.3389/fmicb.2016.01881.

[42] A. Sessitsch *et al.* , "Microbiome Interconnectedness throughout Environments with Major Consequences for Healthy People and a Healthy Planet," *DIGITAL.CSIC (Spanish National Research Council (CSIC))* , vol. 87, no. 3, Jun. 2023, doi: 10.1128/mmbr.00212-22.

[43] C. Díaz-Gavidia, F. P. Álvarez, J. M. Munita, S. Cortés, and A. I. Moreno-Switt, "Perspective on Clinically-Relevant Antimicrobial Resistant Enterobacterales in Food: Closing the Gaps Using Genomics," *Frontiers in Sustainable Food Systems* , vol. 5, May 2021, doi: 10.3389/fsufs.2021.667504.

[44] N. SAISHU, H. Ozaki, and T. Murase, "CTX-M-Type Extended-Spectrum β-Lactamase-Producing *Klebsiella pneumoniae* Isolated from Cases of Bovine Mastitis in Japan," *Journal of Veterinary Medical Science* , vol. 76, no. 8, pp. 1153–1156, Jan. 2014, doi: 10.1292/jvms.13-0120.

[45] C. M. Liu *et al.* , "Escherichia coli ST131- H 22 as a Foodborne Uropathogen," *mBio* , vol. 9, no. 4, Aug. 2018, doi: 10.1128/mbio.00470-18.

[46] C. L. Gorrie *et al.* , "Genomic dissection of Klebsiella pneumoniae infections in hospital patients reveals insights into an opportunistic pathogen," *Nature Communications* , vol. 13, no. 1, pp. 3017–3017, May 2022, doi: 10.1038/s41467-022-30717-6.

[47] K. Marimuthu *et al.* , "Whole genome sequencing reveals hidden transmission of carbapenemase-producing Enterobacterales," *Nature Communications* , vol. 13, no. 1, pp. 3052–3052, Jun. 2022, doi: 10.1038/s41467-022-30637-5.

[48] C. Wu, L. Zheng, and J. Yao, "Analysis of Risk Factors and Mortality of Patients with Carbapenem-Resistant Klebsiella pneumoniae Infection," *Infection and Drug Resistance* , pp. 2383–2391, May 2022, doi: 10.2147/idr.s362723.

[49] S.-K. Chiu *et al.* , "National Surveillance Study on Carbapenem Non-Susceptible Klebsiella pneumoniae in Taiwan: The Emergence and Rapid Dissemination of KPC-2 Carbapenemase," *PLoS ONE* , vol. 8, no. 7, Jul. 2013, doi: 10.1371/journal.pone.0069428.

[50] A. Touati, N. A. Ibrahim, A. Mairi, H. Kirat, N. S. Basher, and T. Idres, "One Health at Risk: Plasmid-Mediated Spread of mcr-1 Across Clinical, Agricultural, and Environmental Ecosystems," *Antibiotics* , vol. 14, no. 5, pp. 506–506, May 2025, doi: 10.3390/antibiotics14050506.

[51] W. C. Shropshire *et al.* , "Systematic Analysis of Mobile Genetic Elements Mediating β-Lactamase Gene Amplification in Noncarbapenemase-Producing Carbapenem-Resistant Enterobacterales Bloodstream Infections," *mSystems* , vol. 7, no. 5, Aug. 2022, doi: 10.1128/msystems.00476-22.

[52] N. Strepis *et al.* , "Genetic Analysis of mcr-1-Carrying Plasmids From Gram-Negative Bacteria in a Dutch Tertiary Care Hospital: Evidence for Intrapatient and Interspecies Transmission Events," *Frontiers in Microbiology* , vol. 12, pp. 727435–727435, Sep. 2021, doi: 10.3389/fmicb.2021.727435.

[53] R. M. Martin and M. A. Bachman, "Colonization, Infection, and the Accessory Genome of Klebsiella pneumoniae," *Frontiers in Cellular and Infection Microbiology* , vol. 8, pp. 4–4, Jan. 2018, doi: 10.3389/fcimb.2018.00004.

[54] Y. Li and R. Farzana, "Mobile genetic elements in shaping Klebsiella pneumoniae pathogenicity," *Oxford University Research Archive (ORA) (University of Oxford)* . University of Oxford, Jan. 01, 2026.

[55] E.-J. Yoon and S. H. Jeong, "Mobile Carbapenemase Genes in Pseudomonas aeruginosa," *Frontiers in Microbiology* , vol. 12, pp. 614058–614058, Feb. 2021, doi: 10.3389/fmicb.2021.614058.

[56] L. Poirel, J. Decousser, and P. Nordmann, "Insertion Sequence IS Ecp1B Is Involved in Expression and Mobilization of a bla CTX-M β-Lactamase Gene," *Antimicrobial Agents and Chemotherapy* , vol. 47, no. 9, pp. 2938–2945, Aug. 2003, doi: 10.1128/aac.47.9.2938-2945.2003.

[57] Y. Li and R. Farzana, "Mobile genetic elements in shaping Klebsiella pneumoniae pathogenicity," *Frontiers in Microbiology* , vol. 16, pp. 1730961–1730961, Jan. 2026, doi: 10.3389/fmicb.2025.1730961.

[58] A. Gomez-Simmonds, M. K. Annavajhala, D. Seeram, T. W. Hokunson, H. Park, and A. Uhlemann, "Genomic epidemiology of carbapenem-resistant Enterobacterales at a New York City hospital over a 10-year period reveals complex plasmid-clone dynamics and evidence for frequent horizontal transfer ofblaKPC," *Genome Research* , vol. 34, no. 11, pp. 1895–1907, Oct. 2024, doi: 10.1101/gr.279355.124.

[59] E. S. Snitkin *et al.* , "Tracking a Hospital Outbreak of Carbapenem-Resistant Klebsiella pneumoniae with Whole-Genome Sequencing," *Science Translational Medicine* , vol. 4, no. 148, Aug. 2012, doi: 10.1126/scitranslmed.3004129.

[60] B. Kitchel *et al.* , "Molecular Epidemiology of KPC-Producing Klebsiella pneumoniae Isolates in the United States: Clonal Expansion of Multilocus Sequence Type 258," *Antimicrobial Agents and Chemotherapy* , vol. 53, no. 8, pp. 3365–3370, Jun. 2009, doi: 10.1128/aac.00126-09.

[61] T. A. Russo and C. Marr, "Hypervirulent Klebsiella pneumoniae," *Clinical Microbiology Reviews* , vol. 32, no. 3, May 2019, doi: 10.1128/cmr.00001-19.

[62] M. A. Winkler *et al.* , "A One Health study of Klebsiella pneumoniae species complex plasmids shows a highly diverse and ecologically adaptable plasmidome," *Microbial Genomics* , vol. 12, no. 2, Feb. 2026, doi: 10.1099/mgen.0.001629.

[63] F. Yang, B. Deng, W. Liao, P. Wang, P. Chen, and W. Jidong, “<p>High rate of multiresistant Klebsiella pneumoniae from human and animal origin</p>,” *Infection and Drug Resistance* , pp. 2729–2737, Sep. 2019, doi: 10.2147/idr.s219155.

[64] C. Xu, L. Kong, H. Gao, X. Cheng, and X. Wang, “A Review of Current Bacterial Resistance to Antibiotics in Food Animals,” *Frontiers in Microbiology* , vol. 13, pp. 822689–822689, May 2022, doi: 10.3389/fmicb.2022.822689.

[65] A. D. Cesare *et al.* , “Treated wastewater: A hotspot for multidrug- and colistin-resistant Klebsiella pneumoniae,” *Environmental Pollution* , vol. 359, pp. 124598–124598, Jul. 2024, doi: 10.1016/j.envpol.2024.124598.

[66] J. Bengtsson-Palme and S. Heß, “Strategies to Reduce or Eliminate Resistant Pathogens in the Environment.” pp. 637–673, Aug. 23, 2019. doi: 10.1002/9781119282549.ch24.

[67] M. A. K. Hetland *et al.* , “A genome-wide One Health study of Klebsiella pneumoniae in Norway reveals overlapping populations but few recent transmission events across reservoirs,” *Genome Medicine* , vol. 17, no. 1, pp. 42–42, Apr. 2025, doi: 10.1186/s13073-025-01466-0.

[68] M. G. Menozzi *et al.* , “Two-Center Collaborative Evaluation of Performance of the BD Phoenix Automated Microbiology System for Identification and Antimicrobial Susceptibility Testing of Gram-Negative Bacteria,” *Journal of Clinical Microbiology* , vol. 44, no. 11, pp. 4085–4094, Nov. 2006, doi: 10.1128/jcm.00614-06.

[69] C. Johnson *et al.* , “Multiplex detection of the big five carbapenemase genes using solid-phase recombinase polymerase amplification,” *The Analyst* , vol. 149, no. 5, pp. 1527–1536, Jan. 2024, doi: 10.1039/d3an01747h.

[70] T. K. Dang, N. T. T. Hà, and A. W. Taylor-Robinson, “ANTIMICROBIAL STEWARDSHIP PROGRAMS,” 2025, pp. 583–618. doi: 10.58532/nbennurndmcsw22.

[71] D. Ben-David *et al.* , “Potential Role of Active Surveillance in the Control of a Hospital-Wide Outbreak of Carbapenem-Resistant Klebsiella pneumoniae Infection,” *Infection Control and Hospital Epidemiology* , vol. 31, no. 6, pp. 620–626, Apr. 2010, doi: 10.1086/652528.

[72] D. H. Lloyd and S. W. Page, “Antimicrobial Stewardship in Veterinary Medicine,” *Microbiology Spectrum* , vol. 6, no. 3, Jun. 2018, doi: 10.1128/microbiolspec.arba-0023-2017.

[73] D. van Duin and D. L. Paterson, “Multidrug-Resistant Bacteria in the Community,” *Infectious Disease Clinics of North America* , vol. 30, no. 2, pp. 377–390, May 2016, doi: 10.1016/j.idc.2016.02.004.

[74] H. Majeed *et al.* , “Evaluation of Metagenomic-Enabled Antibiotic Resistance Surveillance at a Conventional Wastewater Treatment Plant,” *Frontiers in Microbiology* , vol. 12, pp. 657954–657954, May 2021, doi: 10.3389/fmicb.2021.657954.

[75] C. Opoku-Temeng, S. D. Kobayashi, and F. R. DeLeo, “Klebsiella pneumoniae capsule polysaccharide as a target for therapeutics and vaccines,” *Computational and Structural Biotechnology Journal* , vol. 17, pp. 1360–1366, Jan. 2019, doi: 10.1016/j.csbj.2019.09.011.

[76] W. Ding, Y. Wen, L. Chen, and H. Du, “Bacteriophage Therapy Against Klebsiella Pneumoniae,” *Microorganisms* , vol. 14, no. 1, pp. 201–201, Jan. 2026, doi: 10.3390/microorganisms14010201.

[77] D. P. Araya, K. L. Palmer, and B. A. Duerkop, “CRISPR-based antimicrobials to obstruct antibiotic-resistant and pathogenic bacteria,” *PLoS Pathogens* , vol. 17, no. 7, Jul. 2021, doi: 10.1371/journal.ppat.1009672.