Innovations in *Klebsiella pneumoniae* Vaccine Development: Current Progress and Future Prospects

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Abstract

Klebsiella pneumoniae is a Gram-negative bacterium belonging to the family *Enterobacteriaceae.* It causes healthcare and community-acquired infections complicated by multidrug resistance (MDR) and hypervirulence. This review provides a comprehensive overview of the current progress and prospects of vaccine development for *K. pneumoniae*. Several vaccines were explored including next-generation mRNA vaccines and ghost cell vaccines. Each vaccine category and suitable adjuvants was discussed in terms of immunogenicity, safety, production scalability, and stage of development. Despite progress, major challenges incurred are achieving broad strain coverage, avoiding reactogenicity, ensuring mucosal immunity, and simplifying manufacturing. Adjuvant selection, such as alum, CpG, MPLA, and chitosan, plays a critical role in optimizing immune responses. Conjugate and subunit vaccines show strong near-term potential, while mRNA and ghost cell platforms offer exciting long-term prospects. Accelerating these innovations through robust biotechnological infrastructure and scalable production supports SDG 9 by strengthening scientific research, fostering industrial innovation, and building resilient health-related manufacturing capabilities. Advancing these technologies could yield safe, effective, and scalable vaccines to protect high-risk populations against this formidable pathogen.

Key words: SDG 9, vaccines, adjuvants, humoral immunity, cell mediated immunity, efficacy.

Introduction

Klebsiella pneumoniae is a Gram-negative bacillus classified under the family *Enterobacteriaceae.* It is non-motile, does not form spores, and thrives in both aerobic and anaerobic environments. It is commonly associated with both environmental and host-associated habitats, existing as a commensal organism in the host and acts as an opportunistic pathogen under certain conditions. It causes healthcare-associated infections and community-acquired infections (Martin and Bachman, 2018). Infections with *K. pneumoniae* are especially dangerous in vulnerable populations, such as neonates, the elderly and immunosuppressed individuals (Anes *et al.,* 2017). *K. pneumoniae* is a major contributor of infection-related deaths related to antimicrobial resistance, globally (Kot *et al.,* 2023). Particularly, hypervirulent strains of *K. pneumoniae* cause serious infections in humans that are not responsive to treatment (Opoku-Temeng *et al.,* 2022). The limited therapeutic options for these infections emphasize the need for alternative strategies (Huy, 2024). The convergence of hypervirulence and antimicrobial resistance is creating "superbugs" that pose a significant challenge to healthcare (Paczosa and Mecsas, 2016). Vaccines offer a crucial strategy to prevent infections by reducing dependence on use of antibiotics, thereby reducing antimicrobial resistance in a population (Khodayari & Feizi 2017; Bai and Guo, 2024). Vaccines are needed to protect high-risk groups like hospitalized immunosuppressed individuals and neonates (Arato *et al.,* 2021). The development of *K. pneumoniae* vaccines has been recognized as a major public health priority by the World Health Organization (WHO) (Bengoechea and Sa Pessoa, 2019). This review gives a comprehensive and critical overview of the current vaccine development strategies targeting *Klebsiella pneumoniae*, including conventional and next-generation platforms. It also seeks to identify gaps, challenges, and prospects in translating preclinical success into clinical solutions.

Materials and Methods

This review was conducted by systematically searching PubMed, Scopus, and Google Scholar databases for articles published between 2010 and 2025 along with relevant articles published before 2010. The following keywords and their combinations were used for article searching: *"Klebsiella pneumoniae"*, "vaccine development", "conjugate vaccine", "subunit vaccine", "mRNA vaccine", "outer membrane proteins", "bacterial ghost", "adjuvants", and "immunogenicity". Preference was given to peer-reviewed articles, clinical trials, systematic reviews, and recent experimental studies. Some references were taken from the bibliographies of included studies. Articles were selected based on relevance to vaccine development platforms, preclinical or clinical progress, and relevance to public health strategies.

Clinical Significance of *Klebsiella pneumoniae* in Animals: A Veterinary Perspective

Klebsiella pneumoniae is an opportunistic Gram-negative bacterium that infects cattle, buffaloes, sheep, goats, pigs, horses, poultry, and other animal species (Wall *et al.,* 2023; Hou *et al.,* 2024; Kot and Witeska, 2024). It is a major cause of environmental mastitis in dairy animals, leading to udder inflammation, reduced milk yield, poor milk quality, and economic losses (Osman *et al.,* 2014; Liu *et al.,* 2022; Kedir *et al.,* 2026). The increasing occurrence of antimicrobial-resistant *K. pneumoniae* mastitis has also raised concerns regarding zoonotic transmission and public health under a One Health framework (Payros *et al.,* 2026). *K. pneumoniae* has emerged as an important antimicrobial-resistant pathogen in poultry production systems (Kahin *et al.,* 2024). The pathogen also causes pneumonia, septicemia, reproductive disorders, urinary tract infections, wound infections, and arthritis (Chang *et al.,* 2021; Hou *et al.,* 2024; Gravey *et al.,* 2024), particularly in young, stressed, or immunocompromised animals (Chang *et al.,* 2021; Hou *et al.,* 2024).

The infection adversely affects animal health, productivity, and welfare through reduced growth, reproductive losses, increased treatment costs, mortality, and premature culling. Furthermore, animal-derived *K. pneumoniae* frequently carries multidrug-resistant (MDR), ESBL-producing, and carbapenem-resistant genes (Kot and Witeska, 2024; Shamanna *et al.,* 2024), making it an important One Health pathogen and highlighting the need for improved surveillance, antimicrobial stewardship, biosecurity, and vaccine development (Wall *et al.,* 2023; Kot and Witeska, 2024; Pandey *et al.,* 2024). Despite growing evidence of MDR *K. pneumoniae* in livestock, its true burden in Indian production systems remains poorly characterized because routine surveillance is still limited.

Vaccines of *K. pneumoniae*

Several vaccines (Figure 1, Table 1) have been explored against *Klebsiella pneumoniae* (Bengoechea and Sa Pessoa, 2019; Assoni *et al.,* 2021).

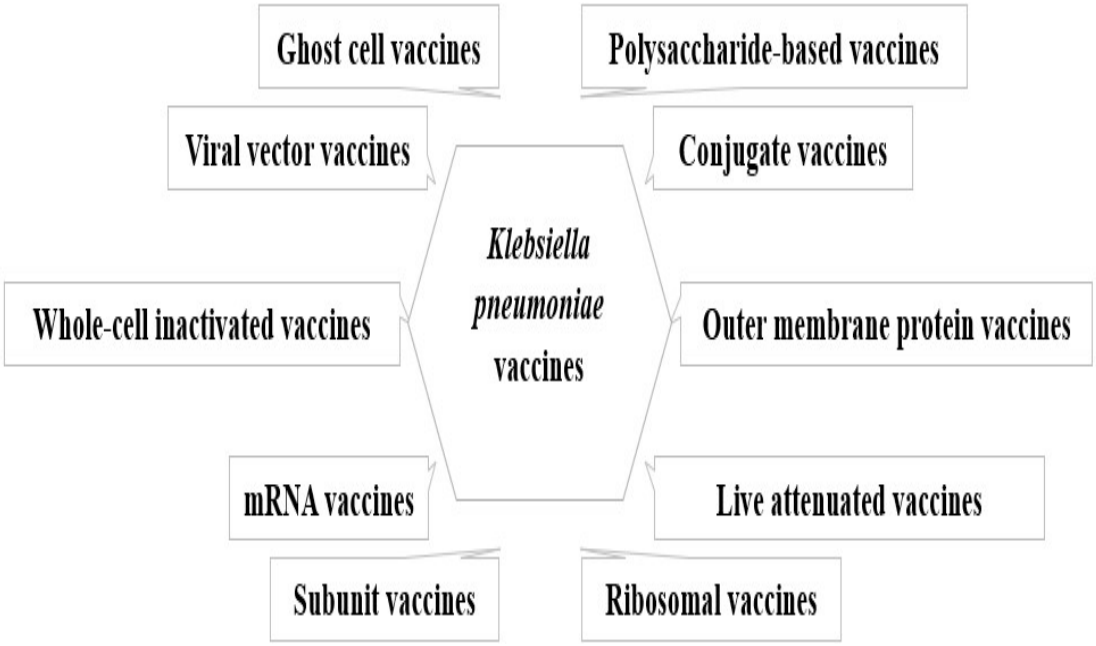

Figure 1: Different types of vaccines of *Klebsiella pneumoniae* under exploration

1. Polysaccharide-based vaccines

These vaccines are capsular polysaccharides (CPS) or lipopolysaccharides, which are major components of the *K. pneumoniae* outer surface and serve as important virulence factors (Miller *et al.,* 2024). These vaccines induce serotype-specific protection and provide broad coverage when multivalent formulations are used to prepare vaccine (Choi *et al.,* 2019). But it has some limitations. It provides only T-cell independent immune response. Hence, it creates poor immunogenicity in infants, elderly, and immunocompromised people. It won't create memory responses because of the non-involvement of T-cells (Opoku-Temeng *et al.,* 2019). Eg. Multivalent CPS vaccine targeting K1, K2, K5, K20, K54, and K57 serotypes (Feldman *et al.,* 2019). Some vaccine candidates are in preclinical studies. Historical pre-clinical studies show that limited long-term efficacy is due to poor immunogenicity. It may be improved with novel adjuvants or nanoparticle carriers (Liu *et al.,* 2023). It can be replaced or combined with conjugate vaccines or other advanced platforms for more efficacy (Lin *et al.,* 2022).

2. Conjugate vaccines

In these vaccines, poorly immunogenic polysaccharide antigens like CPS or LPS were covalently linked to a strongly immunogenic protein carrier to enhance T-cell-dependent immune response (Micoli *et al.,* 2021). Widely used carrier protein in conjugate vaccines is CRM197 (van der Put, 2023). This results in improved immunogenicity in infants and elderly, induction of immunological memory, boosting of IgG antibody responses against polysaccharide capsules and long-term immunity (Assoni *et al.,* 2021; Wang *et al.,* 2025). Manufacturing complexity and limited coverage on diverse pathogenic strains are the major constraints (Feldman *et al.,* 2019). E.g. Bioconjugate vaccine using CRM197 conjugated to K1/K2 CPS (Micoli *et al.,* 2021). Active research is ongoing for multivalent conjugates and synthetic carbohydrate conjugate vaccines (van der Put *et al.,* 2023). Bioconjugate technology can improve scalability and reproducibility (Zhang *et al.,* 2024). The conjugate vaccines can be considered as the strongest near-term candidates for human use, especially for high-risk populations like ICU patients (Feldman *et al.,* 2019). It can be included in hospital-preventive immunization programs in the coming years (Lin *et al.,* 2022).

3. Outer Membrane Protein (OMP) vaccines

This vaccine is prepared by targeting conserved proteins embedded in the outer membrane such as OmpA, OmpK36, which are involved in structural integrity and iron uptake (Shahbazi et al., 2023). Conserved proteins across different strains of *K. pneumoniae* are needed for cross protection. It induces both humoral and cellular immunity (Zhang *et al.,* 2021). Strong adjuvants are required for good immunogenicity (Hussein *et al.,* 2018). There may be a risk of autoimmune response if cross-reactivity occurs. The structural complexity of membrane proteins can affect stability of vaccine (Assoni, *et al.,* 2021). Eg. Recombinant OmpA vaccine in mice showed protection across several strains. Kpn_Omp001, Kpn_Omp002, Kpn_Omp005-recombinant OMPs protective in mice (Zhang *et al.,* 2021). Glyco-bioconjugate- candidate effective in mice (Babu *et al.,* 2017; Avila-Calderón et al., 2021). Immunoproteomics can be used to identify cross-strain antigens (Hussein *et al.,* 2018). It is considered a good candidate for cross-protective or universal vaccines (Liu *et al.,* 2022). The combined vaccine

prepared from OMPs and other subunits of bacterial cell wall will be considered for potential vaccine candidate (Assoni, *et al.,* 2021).

4. Live attenuated vaccines

These vaccines were prepared from live, genetically engineered strains of *K. pneumoniae* with deleted or disabled virulence genes (knock out rmpA, magA, entB, or capsule genes) (Hsieh *et al.,* 2014; Zhang *et al.,* 2022). It could elicit strong and broad immune responses including mucosal immunity (Moscoso *et al.,* 2022*)*. It could provide long-lasting protection due to antigenic diversity of live organisms (Malachowa *et al.,* 2019). The major safety concern is that there are possibilities of reversion of virulence by these vaccine strains (Assoni *et al.,* 2021). It is not suitable for immuno-compromised individuals (Ljungman *et al.,* 2012). Strict biosafety protocols should be followed while preparing live attenuated vaccines. Eg. rmpA/magA-deleted hypervirulent strains tested in mice (Hsieh *et al.,* 2014). Most of the developed live attenuated vaccines are in animal model testing stages. It could be used in oral or intranasal mucosal vaccines if attenuation is proven safe (Moscoso *et al.,* 2022).

5. Ribosomal vaccines

These are a type of subunit vaccines that use purified ribosomes or ribosomal proteins from bacteria as immunogenic components (Paśnik, 2016). These vaccines contain broad -spectrum antigens that can stimulate both humoral and cellular immunity and offer wide protection against different strains of *K. pneumoniae* (Oleszycka and Lavelle, 2014). The most technical challenge for these vaccines is standardization and purity (Assoni *et al.,* 2021). Eg. Experimental ribosomal vaccines showed immune response in early mouse studies. These vaccines are in early preclinical or experimental phases. It has potential for broad-spectrum or cross species vaccines (eg. covering other Enterobacteriaceae) (Bolourchi *et al.,* 2022).

6. Subunit vaccines

These vaccines are prepared by purified or recombinant bacterial components such as iron acquisition systems (IroN, YbtA), fimbrial adhesins (FimH), or capsule synthesis proteins (Wzi, Wza) (Peng *et al.,* 2021; Assoni *et al.,* 2025). It requires adjuvants for desired immune responses (Micoli *et al.,* 2018, Rodrigues *et al.,* 2020). These are highly defined and safe vaccines, because there is no direct involvement of bacteria. Minimal off-target effects can be seen due to the target-specific nature of these vaccines. These can be combined in multivalent formulations (Assoni *et al.,* 2021). There will be a chance of missing protective epitopes in the vaccine preparation (Opoku-Temeng *et al.,* 2022). Eg. Subunit vaccine based on siderophore receptors shown to protect mice (Peng *et al.,* 2021). Multiple vaccine candidates are in preclinical phases. There are several patents filed, and animal studies published in this area (Rafi *et al.,* 2023). It is the most promising platform for custom multivalent vaccines. It is compatible with mRNA, nanoparticles, and adjuvant delivery systems (Assoni *et al.,* 2021).

7. mRNA vaccines

These vaccines are composed of messenger RNA (mRNA) that triggers an immune response to protect against future infection (Sahin *et al.,* 2014). The constructed mRNA molecules are delivered into host cells using lipid nanoparticles (Pardi *et al.,* 2018). Broad protection against pathogen is possible with delivering conserved antigens of multiple strains or serotypes in this vaccine preparation (Huang *et al.,* 2025). Rapid design and modification of vaccine, scalability, no live pathogen involvement and potential to develop multivalent formulations quickly are the advantages (Pardi *et al.,* 2018). Cold chain logistics are essential to maintain stability of the vaccine candidate (Kis, 2022). Currently no mRNA vaccine for any bacterial infection approved yet (Blakney *et al.,* 2021). This type of vaccine is still in experimental and preclinical testing phases with respect to *K. pneumoniae* (Huang *et al.,* 2025). Next-gen platforms may allow multivalent or pan-pathogen mRNA vaccines (Rodrigues *et al.,* 2020).

8. Whole cell inactivated vaccines

These vaccines are formalin or heat killed whole bacteria cells, contain all surface and intracellular antigens and often combined with adjuvants like alum or CpG (Assoni *et al.,* 2021). It brings more exposure of the immune system to a broad range of antigens (LPS, OMPs, CPS) (Kawser *et al.,* 2021). Simple to produce, low cost to produce and broad antigen presentation are the advantages of this system. Its use is discontinued due to risk of strong inflammatory responses and batch consistency issues (Assoni *et al.,* 2021). There will be a higher risk of reactogenicity and adverse effects with these vaccine candidates (Lv *et al.,* 2024). It may not induce long lasting immunity. Immune response for this type of vaccine is dominated by non-protective antigens (Choi *et al.,* 2019).

9. Viral vector vaccines

These vaccines contain a genetically modified, non-replicating viral vector to deliver antigens encoding genes into the host cells (Motamed *et al.,* 2024). These host cells produce antigen that triggers an immune response and mimic natural infection pathways which includes CD8+ cytotoxic T cell responses, long-lasting antigen expression and long-lasting memory (Travieso *et al.,* 2022). It doesn't need adjuvant to improve potency and

efficacy and can be delivered via mucosal (intranasal/oral) routes (De Gregorio and Rappuoli, 2014). Pre-existing immunity towards common viral vectors by humans, antigen misfolding issues, and rare risk of vector induced autoimmunity are the limitations (Micoli *et al.,* 2018). Eg. Adenovirus-based vaccine, Newcastle disease virus-based vaccine. No licensed viral vector vaccines exist yet for *K. pneumoniae* and most viral vector vaccines are in early experimental stages (Motamed *et al.,* 2024).

10. Ghost cell vaccines

These are a type of inactivated bacterial vaccines composed of empty, non-living cell envelopes of bacteria. These are produced by controlled lysis of bacteria without disturbing outer membrane structures and native surface antigens of bacterial cell wall and selectively removing the cytoplasmic content and genetic material (Hetta *et al.,* 2026). These ghost cells retain immunologically important cell wall components of the bacteria. This allows the structural preservation of ghost cells that mimic live bacteria. This is the reason for the induction of both humoral and cellular immune responses, without the risk of infection or replication (Ma *et al.,* 2022). PhiX174 lysis gene E mediated method is the most common method used for Ghost cell preparation (Hetta *et al.,* 2026). Other methods employed for the ghost cell preparation are chemical lysis method (Menisy *et al.,* 2017), thermal lysis method, physical lysis method using ultrasound, and enzymatic lysis method. Eg. Gene E-mediated ghosts tested in mice.

Important adjuvants of *K. pneumoniae vaccines*

Adjuvants are immunostimulatory agents added to vaccines for defined functions (Reed *et al.,* 2013). These enhance magnitude and duration of immune responses, promote humoral and cellular immunity, improve cross protection across serotypes and allow dose sparing and better vaccine efficacy (Chen *et al.,* 2024). These are the following adjuvants used for *K. pneumoniae vaccines.*

1. Aluminum based adjuvants

Aluminum based adjuvants are commonly called alum which include aluminum hydroxide, aluminum phosphate, or alum salts (He *et al.,* 2015). The most widely used vaccine adjuvants are alum-based adjuvants (Shah *et al.,* 2016). Alum favors a Th2 immune response that promotes high IgG1, IgE antibody production and eosinophilic activation (Oleszycka and Lavelle, 2014). But it does not promote strong Th1 or Th17 responses, which are necessary cellular immunity (De Gregorio *et al.,* 2013). Alum is often used in subunit or conjugate vaccines (Pulendran *et al.,* 2021). Eg. OmpA+alum-based vaccine.

2. CpG Oligodeoxynucleotides

These are the unmethylated CpG motifs (cytosine-phophate-guanine dinuclotides) containing synthetic single stranded DNA molecules that mimic bacterial and viral DNA (Scheiermann and Klinman, 2014). These types of adjuvants induce Th1-biased immune response by plasmacytoid dendritic cells via TLR-9 receptor recognition (Kayraklioglu *et al.,* 2020). Strong cellular immunity and enhanced memory are the advantages (Scheiermann and Klinman, 2014). Mostly used in DNA vaccines and subunit vaccines (Yang *et al.,* 2023). Among the CpG ODNs (Class A, Class B, Class C) (Xing *et al.,* 2025), Class B CpG-ODNs are most frequently used for their strong Th1-biasing effect (Scheiermann and Klinman, 2014).

3. Monophosphoryl lipid A (MPLA)

These are the components of LPS of *Salmonella Minnesota* (detoxified derivative of LPS) and act as TLR 4 agonist (Didierlaurent *et al.,* 2017). It activates innate immunity and promotes balanced Th1/Th2 lymphocytes (Reed *et al.,* 2013). Mostly used in mRNA, protein subunit, and conjugate vaccine preparations (Pulendran *et al.,* 2021). Several MPLA vaccine preparations are FDA approved because of its higher safety (Didierlaurent *et al.,* 2017).

4. Chitosan

Chitosan is a cationic, biodegradable, biocompatible, natural polysaccharide derived from the chitin of the crustaceans, widely used to enhance mucosal delivery (oral, nasal, pulmonary) and antigen uptake (Sun *et al.,* 2018). Variable efficiency in humans is the limitation (Smith *et al.,* 2014). Eg. OmpA + chitosan nanoparticles showed increased secretion of nasal IgA and systemic IgG (Omidian *et al.,* 2024).

5. Poly I:C

Polyinosine-polycytidylic acid (Poly I:C) is a double-stranded RNA synthetic analogue that mimics viral genetic material (Desai *et al.,* 2025). It acts as TLR3 agonist and elicits potent immunostimulatory responses (Pulendran *et al.,* 2021). There is a risk of inflammation at high doses with this adjuvant (Hafner *et al.,* 2013). It is mostly used in DNA and mRNA vaccines (Martins *et al.,* 2015). Eg. OmpA DNA vaccine + Poly I:C.

6. Quil-A/ QS-21

These are saponin-based adjuvants that are highly potent immunostimulants in terms of humoral and cell-mediated immune responses (Hu *et al.,* 2025). It enhances antigen presentation and CTL activation (Marciani,

2018). Limited natural availability, cost of procurement and reactogenicity are the challenges (Talukdar *et al.,* 2025). In protein subunit and conjugate vaccines, this type of adjuvants is mostly used (Del Giudice *et al.,* 2018).

7. Cytokine adjuvants

These are soluble signaling molecules used to improve the immunogenicity of an antigen (Pavot *et al.,* 2012). They mimic natural immune signaling and directly modulate immune cell behavior to guide, amplify, or polarize the immune response (Pulendran *et al.,* 2021). Overstimulation can occur if not properly controlled (Liu, 2019). Mostly used in DNA vaccines and protein subunit vaccines for immune modulation (Liu, 2019). Eg. IL-12, GM-CSF adjuvants

8. MF59 (Squalene based emulsion)

It is an oil-in-water type of emulsion-based adjuvant (Garçon *et al.,* 2012). It is squalene-based adjuvant, works by enhancing both innate and adaptive immunity (O'Hagan *et al.,* 2013). Mostly seen in injectable subunit vaccines (Del Giudice *et al.,* 2018).

9. Bacterial ghosts (Natural Immunopotentiators)

These are safe, non-replicative, self-adjuvanted empty cell envelopes produced by controlled lysis of Gram-negative bacteria, typically using the bacteriophage lysis gene E (Dentovskaya *et al.,* 2025). They retain the intact outer membrane structure, surface antigens, and pathogen-associated molecular patterns (PAMPs), devoid of cytoplasmic contents and genetic material (Dentovskaya *et al.,* 2025). They are used both as adjuvants and vaccine delivery systems (Chen *et al.,* 2021). They induce strong innate and adaptive immunity (Hajam *et al.,* 2017). Mostly used in whole-cell vaccines and GMMA or OMV-based vaccines (Gan *et al.,* 2023). Eg. OMV vaccine from *K. pneumoniae* with no extra adjuvant showed effective protection in experimental models (Tan *et al.,* 2018).

Table 1: Status and prospects of *K. pneumoniae* vaccines (Assoni *et al.,* 2021)

Vaccine Type	Current Status	Prospective developments
Polysaccharide	Preclinical	Limited; likely to be combined with conjugates. Reported efficacy is ~60% in mouse models
Conjugate	Phase I/II Clinical Trials	High; near-term deployment possible. 70-90% efficacy in murine models achieved.
OMP	Preclinical	Strong cross-protection potential. 60-85% efficacy reported in mouse models.
Live Attenuated	Animal studies	Research/vet use; biosafety improvements needed. 85% efficacy observed in sepsis models.
Ribosomal	Experimental	Broad-target vaccine research. Variable efficacy reported.
Subunit	Preclinical	Excellent potential; flexible and safe. Up to 80% efficacy reported
mRNA	Early preclinical	High-tech, scalable, customizable but efficacy not yet quantified
Whole-Cell Inactivated	Mostly historical	Low prospects due to safety concerns. High reactogenicity, low durability are the features
Ghost cell	Preclinical	No human clinical trials have been reported as of now.

Global Status of *K. pneumoniae* Vaccine Development

World Health Organization Priority Classification

The World Health Organization (WHO) identifies antibiotic-resistant bacteria that pose the greatest threat to public health and require urgent attention for research, drug development, surveillance, and infection-control measures (World Health Organization, 2024). The pathogens are classified into Critical, High, and Medium Priority categories based on mortality, incidence, disease burden, resistance trends, transmissibility, preventability, treatability, and the availability of new therapeutic options. *Klebsiella pneumoniae* is included within carbapenem-resistant and third-generation cephalosporin-resistant Enterobacterales, both belonging to the Critical Priority category (World Health Organization, 2024). This critical priority designation has accelerated the clinical vaccine pipeline, with several candidates now entering human trials.

Current Clinical Trial Pipeline

Although no licensed vaccine is currently available, the clinical pipeline is expanding rapidly, with O-antigen and capsule-based candidates advancing into human trials. Kleb4V has become the first candidate to demonstrate safety and immunogenicity in human trials (Alaimo *et al.,* 2026), while CHO-V08 has entered Phase I evaluation (Hu *et al.,* 2026). Although multivalent O-antigen and capsule-based glycoconjugate vaccines have shown promising immunogenicity, their long-term effectiveness against the extensive antigenic diversity observed among global and Indian isolates remains uncertain (Douradinha, 2024; Shamanna *et al.,* 2024; Wantuch *et al.,* 2024). Promising vaccine platforms in preclinical development are multivalent O-antigen bioconjugate vaccines (VaxNewMo and collaborators), heptavalent O-antigen vaccines covering a broader range of clinical isolates, K1/K2 capsule-based glycoconjugate vaccines for hypervirulent strains (Wantuch *et al.,* 2025), Outer Membrane

Vesicle (OMV) vaccines (Lee *et al.,* 2015) and protein-antigen vaccines targeting fimbrial and conserved virulence proteins (MrkA, FepA, etc.) (Douradinha, 2024).

Kleb4V and Other Advanced Vaccine Candidates

Kleb4V and CHO-V08 are the most advanced *Klebsiella pneumoniae* vaccine candidates currently in clinical development, representing two complementary vaccine strategies. Kleb4V, developed by LimmaTech Biologics and GSK, is a tetravalent bioconjugate vaccine targeting the O1v1, O2a, O2afg, and O3b O-antigen serotypes, providing broad protection against invasive and multidrug-resistant *K. pneumoniae* infections. It has completed Phase I/II trials and demonstrated good safety and strong immunogenicity (Alaimo *et al.,* 2026). In contrast, CHO-V08, developed by CHO Pharma, is a bivalent glycoconjugate vaccine targeting the K1 and K2 capsular serotypes associated with hypervirulent strains (Hu *et al.,* 2026) that cause liver abscesses, meningitis, and severe invasive disease. Currently in Phase I clinical evaluation, CHO-V08 aims to prevent hypervirulent *K. pneumoniae* infections. Unlike capsule-based vaccines such as CHO-V08 that primarily target hypervirulent strains, O-antigen-based candidates such as Kleb4V aim to achieve broader strain coverage. However, the relative contribution of these approaches to population-level protection remains unclear (Douradinha, 2024; Hu *et al.,* 2026). An additional challenge is that antigen prevalence varies considerably across geographic regions, raising uncertainty regarding the global applicability of a single vaccine formulation.

***K. pneumoniae* Vaccine Development: India's Perspective**

Genomic Surveillance of Indian Isolates

Genomic surveillance of *Klebsiella pneumoniae* in India has revealed extensive genetic diversity and a high prevalence of multidrug-resistant (MDR) and carbapenem-resistant strains. Whole-genome sequencing studies have identified major high-risk clones, including ST231, ST147, ST14, ST11, and ST15 (Shamanna *et al.,* 2024), circulating in healthcare settings. Resistance genes such as blaOXA-232, blaOXA-181, and blaNDM are widely distributed (Shamanna *et al.,* 2024) and are often carried on mobile plasmids, facilitating their spread.

Surveillance efforts by the Indian Council of Medical Research and other research institutions have also mapped capsular (K) and O-antigen diversity among Indian isolates (Shamanna *et al.,* 2024). Additionally, some strains exhibit both antimicrobial resistance and hypervirulence traits, posing a major public health concern (Shamanna *et al.,* 2024). These genomic data are crucial for monitoring pathogen evolution, guiding infection-control measures, and supporting the development of broadly protective *K. pneumoniae* vaccines (Shamanna *et al.,* 2024).

Preclinical Advances (DFRL r-AK36 Candidate)

r-AK36 is a recombinant multi-epitope subunit vaccine developed by DFRL-DRDO, Mysuru, using conserved outer membrane proteins OmpA and OmpK36 of *Klebsiella pneumoniae*. Preclinical studies in mice demonstrated strong antibody and cellular immune responses, inhibition of biofilm formation, and approximately 80–83% protection against lethal bacterial challenge (Babu *et al.,* 2017). While r-AK36 demonstrated encouraging protection in murine models, its efficacy against genetically diverse clinical isolates and its translational potential in humans remain to be established (Babu *et al.,* 2017).

Gaps and Future Directions for India

A major challenge in India is the high capsular (K) and O-antigen diversity of *K. pneumoniae*, which limits the coverage of current vaccine candidates. Most Indian vaccine research remains at the preclinical stage, and protective immune correlates are not yet fully understood (Shamanna *et al.,* 2024; Douradinha, 2024). In addition, nationwide One Health surveillance integrating human, animal, and environmental isolates is still limited.

Future efforts should focus on developing multivalent or universal vaccines using conserved protein antigens and prevalent capsular/O-antigens (Douradinha, 2024; Hu *et al.,* 2026). Expanded genomic surveillance, application of advanced platforms such as mRNA and nanoparticle vaccines (Hu *et al.,* 2026), and stronger collaboration between academia, industry, and government agencies will be essential to accelerate clinical development and achieve broad protection against diverse Indian strains. A major unresolved question is whether conserved protein antigens alone can provide sufficient protection against both carbapenem-resistant and invasive lineages (Douradinha, 2024; Hu *et al.,* 2026). Nevertheless, recent progress in glycoconjugate, protein-subunit, and nanoparticle-based platforms provides a strong foundation for future vaccine strategies (Assoni *et al.,* 2021). From a veterinary perspective, the increasing recovery of MDR *K. pneumoniae* from livestock and poultry underscores the importance of integrating animal surveillance into national antimicrobial-resistance monitoring programs (Wall *et al.,* 2023; Pandey *et al.,* 2024).

Conclusion

Klebsiella pneumoniae poses a significant public health challenge due to its increasing multidrug resistance and the emergence of hypervirulent strains. Despite substantial advances in genomic surveillance and vaccine design, currently no licensed vaccine is available against *K. pneumoniae*. The remarkable antigenic

diversity of the pathogen, coupled with the emergence of antimicrobial-resistant hypervirulent clones, continues to challenge vaccine development. Significant progress has been made in developing various vaccine platforms, including conjugate, subunit, outer membrane protein, ghost cell, and mRNA-based candidates. These approaches show promise in preclinical and early clinical studies. Conjugate and subunit vaccines have emerged as the most promising near-term candidates for preventing *K. pneumoniae* infections. The current clinical frontiers in *K. pneumoniae* vaccines are Kleb4V and CHO-V08. Future vaccine development should focus on creating multivalent, cross-protective, safe, and scalable formulations. Special attention is needed for targeting high-risk groups and improving mucosal immunity in humans as well as animals. The zoonotic spread potential of hypervirulent, multi-drug-resistant *K. pneumoniae* is to be considered in the vaccine development.

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Authors' contributions

K. Harish conceptualized the study, conducted an in-depth literature review, and drafted the initial manuscript. K. Ganesh, contributed to the critical evaluation of vaccine development platforms and assisted in writing the section on current technological innovations. P. Avinash provided inputs on adjuvants used for vaccine preparation. G. Sai Kumar reviewed immunological strategies and supported data organization, figure/table design, and reference validation. P. I. Ganesan, guided the overall development of the draft and provided critical comments on the manuscript for improvement.

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