IDENTIFYING *Klebsiella pneumoniae* VACCINE CANDIDATES THROUGH PAN-GENOMICS

A. Bibi[1], S. M. Bakhtiar[1*], S. A. Jan[1*], S. Tabassum[1] and Neeli Habib[2]

[1]Department of Bioinformatics and Biosciences, Capital University of Science and Technology, Islamabad, Pakistan.
[2]Department of Microbiology, Shaheed Benazir Bhutto Women University Peshawar, Khyber Pakhtunkhwa, Pakistan
*Corresponding author's email: sjan.parc@gmail.com; marriam@cust.edu.pk

ABSTRACT

The rise of multidrug-resistant *Klebsiella pneumoniae* strains and the lack of licensed vaccines highlight the urgent need for effective immunization strategies. The pan-genome analysis was performed to find out the core proteins of *K. pneumoniae* using reverse vaccinology approaches. Selected core proteins based on subcellular localization, antigenicity, transmembrane features, and physicochemical properties help to identify potential vaccine candidates. Pan-genomic analysis of 154 complete *K. pneumoniae* proteomes revealed 15,319 protein families, of which 3,864 were classified as core proteins, reflecting the extensive genetic diversity of the species. Eight proteins involved in drug efflux, toxin export, small molecule diffusion, and bacterial adhesion (pilus assembly). Among these, three proteins involved in drug efflux and toxin export, four proteins involved in facilitating the passive diffusion of small molecules, one outer membrane protein involved in pilus assembly and bacterial adhesion. 3D structures of candidates were experimentally confirmed. The identified epitopes were predicted to be on the protein's surface and capable of MHC I and II binding, suggesting they could initiate an immune response. The identified epitopes suggest the feasibility of developing peptide-based vaccines. By integrating methods, we can create a peptide antigen library for broad or multiple *K. pneumoniae* vaccines.

Keywords: *Klebsiella pneumoniae*. pan-genomics. reverse vaccinology. potential vaccine candidates. epitopes

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Received: April 02 , 2026 Published Online: November 01, 2026 https://doi.org/10.36899/JAPS.2027.1.0012

INTRODUCTION

Klebsiella pneumoniae is categorized as a Gram-negative, encapsulated, non-motile, opportunistic pathogen that causes nosocomial infections like pneumonia, liver abscesses, soft-tissue infections, and urinary tract infections (Joseph *et al.,* 2021). *K. pneumoniae* affects immunocompromised patients and has been linked to individuals with alcohol-related disorders and diabetic patients suffering from pneumonia (Bengoechea and Sa Pessoa, 2019). The bacteria typically inhabit moist areas of the human body, especially the oropharynx and the mucosa of the gastrointestinal tract. *K. pneumoniae* exhibits multi-drug resistance (Chang *et al.,* 2021). Currently, it is considered the most common pathogen responsible for hospital-acquired pneumonia, accounting for approximately 10% of all nosocomial bacterial infections (Asri and Ain, 2021). The mechanisms of resistance identified involve the production of beta-lactamases including carbapenemases, cephalosporinases, and extended-spectrum β-lactamases, which enable the bacteria to survive in nosocomial environments. This resistance is further facilitated by the ongoing horizontal transfer of antibiotic resistance genes (Priyanka, 2020; Angelis, 2020).

K. pneumoniae has emerged as one of the most clinically significant multidrug-resistant (MDR) pathogens worldwide and is recognized by the World Health Organization (WHO) as a critical priority pathogen due to its increasing resistance to carbapenems and third-generation cephalosporins (WHO, 2025). One of the most efficient ways to prevent infection by *K. pneumoniae* is to locate and eradicate its source. Its spread can be control by multi-modal intervention, identification, education, and extensive screening. Identifying affected people and taking all necessary measures, such as donning masks, gowns, and gloves, are important aspects of exposure avoidance (Georgiou and Kotze, 2023).

To minimize future exposure to uninfected individuals, contact tracing should be implemented wherever feasible, in both hospital and community settings. Additionally, healthcare professionals must be educated on the importance of hand hygiene (Georgiou and Kotze, 2023). The development of drug resistance in *K. pneumoniae* is also a concern, often resulting from mechanisms such as biofilm formation, efflux pump activity, and the production of β-lactamases (Turkel *et al.,* 2018).

The pangenomics-based reverse vaccinology pipeline provides a rapid, cost-effective, and systematic framework for vaccine target discovery, offering substantial advantages over conventional vaccinology approaches (Abdelouahab and Idrissa, 2026). The development of a potent vaccine candidate against infectious diseases has been facilitated through the integration of bioinformatics with subtractive genomics and immunoinformatics techniques (Rasool *et al.,* 2024). Due to the lack of comprehensive research for identifying *K. pneumoniae* vaccine candidates via pan-genomics, this study utilized pan-genome analysis to pinpoint conserved core proteins among different *K. pneumoniae* strains, enabling the selection of suitable vaccine candidates and the identification of exposed antigenic epitopes that can bind to MHC I and II molecules.

MATERIALS AND METHODS

Sequence retrieval and quality assessment: A total of 154 *K. pneumoniae* genome sequences, including complete and draft genomes, were retrieved from the PATRIC database (https://www.bv-brc.org/). Among these, 126 complete genomes from global sources and 28 genomes from Pakistan were selected for analysis. All genomes were downloaded from NCBI GenBank (https://www.ncbi.nlm.nih.gov/assembly/). The quality of all strains was analyzed using CheckM v1.2.2 as an essential quality check and low-quality sequences were discarded from the dataset. Only genomes with completeness ≥ 95% and contamination ≤ 5% were retained.

Structural annotation of genome: The assembled genomes were subjected to structural annotation using the Prokka pipeline v 1.14.6 with default parameters. This process produced several output files, including a Protein FASTA file, a Nucleotide FASTA file, and an annotation file in GFF3 format. Subsequently, functional annotation was performed using the Rapid Annotation using Subsystem Technology (RAST) server. The resulting annotation outputs were generated in GenBank and EMBL formats.

Pan-genome Analysis: For the pan-genome analysis, genomic data were obtained from the Pathosystems Resource Integration Center (PATRIC). A total of 140 quality-filtered Klebsiella pneumoniae genomes (128 global and 12 from Pakistan) were used for pan-genome analysis within the Pan Genome Module of the Pan RV pipeline using Roary v3.13.0. Roary was configured to process GFF3 files, with the output options and the percentage identity set to 90%, while other parameters were left at their default settings. The analysis aimed to identify core and accessory genomes across the sampled strains, with the threshold 99% classified as core genes, and used an input value for the subsequent reverse vaccinology analysis

Sub-cellular localization: Regarding membrane location of the potential vaccines, all regions were defined with high confidence using PSORTb v 3. 0 of Pan RV. Selected proteins included proteins that are part of the outer membrane and those found in the extracellular regions. In addition, the proteins whose locations were unknown were further filtered by version 3.0 of PSORTb (https://www.psort.org/psortb/index.html).

Host Homology: To minimize the risk of autoimmune diseases, three steps are taken with the core proteome: 1) human homology as well as 2) gut homology investigation. To filter out the minimum level of similarity based on Swiss-Prot BLAST and RefSeq, PanRV pipeline extends itself to find the human homologs. For the human gut flora safety, the exclusion criteria used was: % identity > (35%) Bit score > 100 and E-value < 1.

Trans-membrane Helices: The number of transmembrane helices in non-host-homologous core proteins was further purified using the HMMTOP v.2.0 (http://www.enzim.hu/hmmtop/html/submit.html). Selected proteins with fewer than 2 transmembrane helices were retained, indicating better surface accessibility and antigenicity than the multi-pass membrane proteins.

Essentiality and Virulence Assessment: K. pneumoniae essential survival genes were identified using BLASTp against the Database of Essential Genes (DEG). virulence factors were assessed through BLASTp against the VFDB. the exclusion criteria used were: % identity > 30%, bit score ≥ 100, and E-value < 1.

Molecular weight determination: The putative antigens with molecular weight less than 110 kDa are chosen for vaccine development with the help of built-in JAVA program.

Similarity to gut flora proteins: Smart-BLAST was utilized to conduct a homology search of the gut flora for essential proteins. Any candidate antigen that exhibited more than 70% homology to a gut flora protein was excluded.

Functional annotation: BLASTp was employed for detailed functional annotation. Proteins exhibiting 100% similarity, complete query coverage, and low E-values ($\leq 1x10^{-5}$) were retained to ensure accurate and reliable annotation

Subtractive epitope scrutinization: In silico prediction of B and T cells epitopes

B cells and T cells epitopes were predicted by using B cell epitope prediction tools (http://tools.iedb.org/main/bcell/) and T cell epitope prediction tools (http://tools.iedb.org/main/tcell/) respectively.

Protein Antigenicity: The antigenicity of the proteins was analyzed by using Antigen-Pro and VaxiJen v.2.0 software. Candidate antigens were considered potential if they had prediction score greater than 0.5.

Predicting Allergenicity of T Cell Epitopes: The T cell epitopes were used to predict allergenicity by using AllerCatPro. T cell epitopes were then further analyzed for toxicity using ToxinPred. (http://crdd.osdd.net/raghava/toxinpred/).

Prediction and visualization of epitope structure: The PEP-FOLD3 web portal was employed to check three-dimensional structures of the selected epitopes, providing predictions and further confirmation. Following this, the identified epitopes were computationally mapped to determine their spatial locations within the protein structures. These epitopes were subsequently visualized using UCSF Chimera 1.1. The detailed methodology is illustrated in Figure 1.

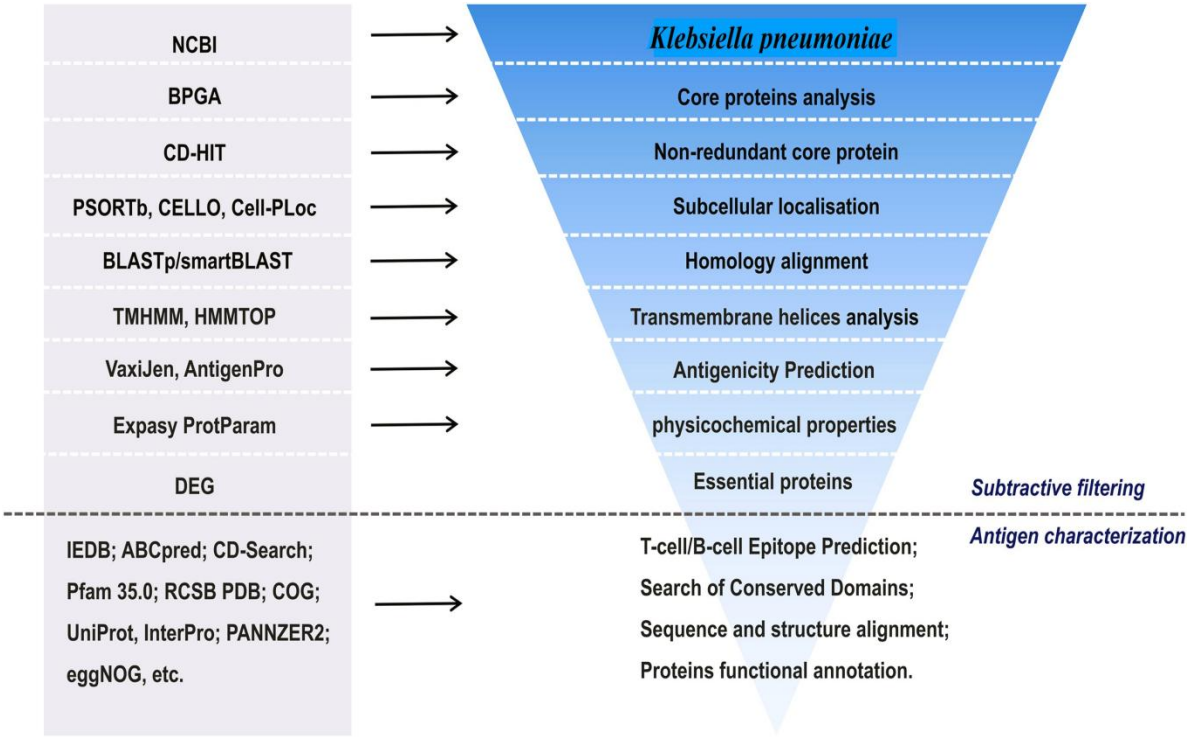

Figure 1. Overview of Methodology.

RESULTS

Pan-genome analysis: A comprehensive analysis was conducted on 154 *K. pneumoniae* genomes retrieved from NCBI on 27 May 2024, comprising 126 completely sequenced and 28 draft genomes. The average genome size across these strains was approximately 5.5 Mb. The GC content of the pathogenic strains was estimated at roughly 50%. Pan-genome analysis using the PanRV tool identified a total of 15,319 genes. It comprises 3864 core genes, which indicates the core genome comprises 25.2 % of the total pan-genome. These gene distributions are depicted in Figures 2 and 3. Further, the pan-genome analysis revealed that *K. pneumoniae* possesses an open pan-genome, with the total number of genes and the number of unique genes increasing as more genomes are added (Figures 4, 5, and 6). Using Roary, a pan-genome matrix was generated, illustrating core proteins in solid blue, alongside a phylogenetic tree. Roary's outputs include a frequency graph and an open pan-genome curve, demonstrating that while the total gene count expands with additional genomes, the number of conserved genes decreases, reinforcing the open nature of the *K. pneumoniae* pan-genome (Figure 5). This analysis provides insights into the genetic diversity of *K. pneumoniae*, aiding in understanding the impact of genetic variants and supporting the development of targeted treatments for conditions associated with specific genomic features.

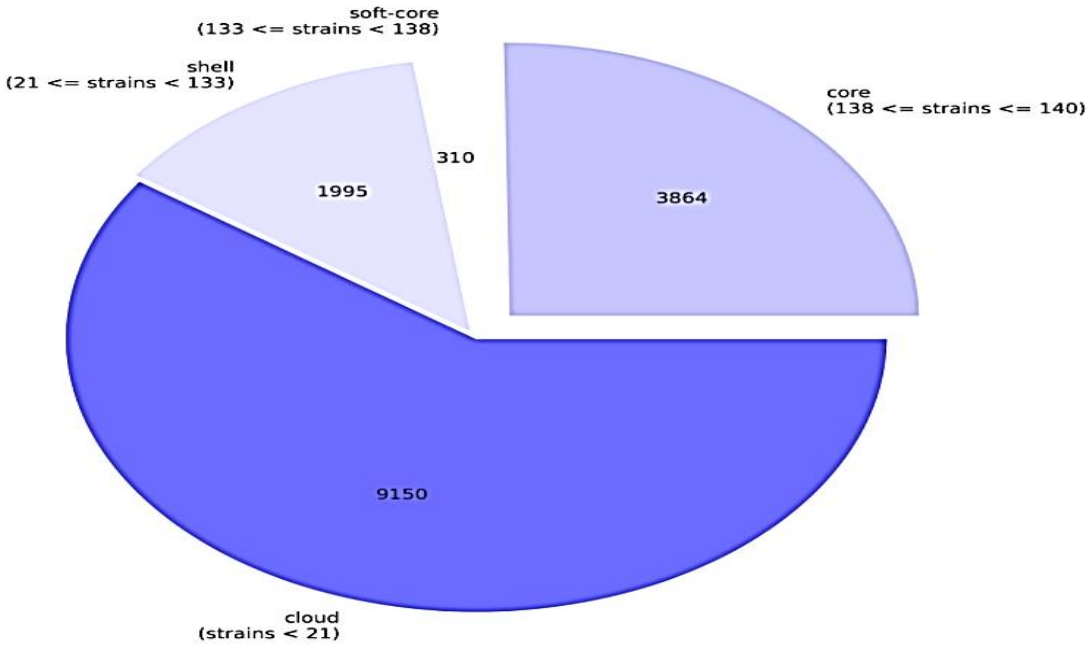

Figure 2. Gene clusters in *K. pneumoniae* pan-genome shows core genes, soft core genes and accessory genes.

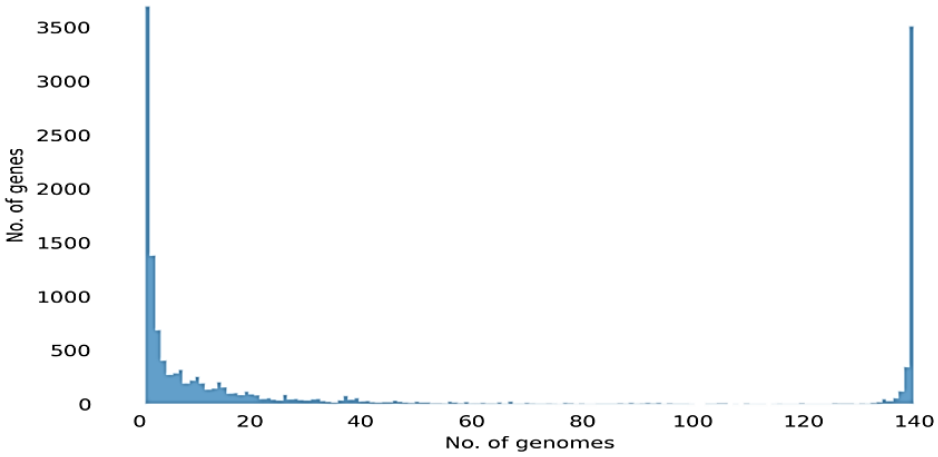

Figure 3. Global genome frequency overview of *K. pneumoniae*

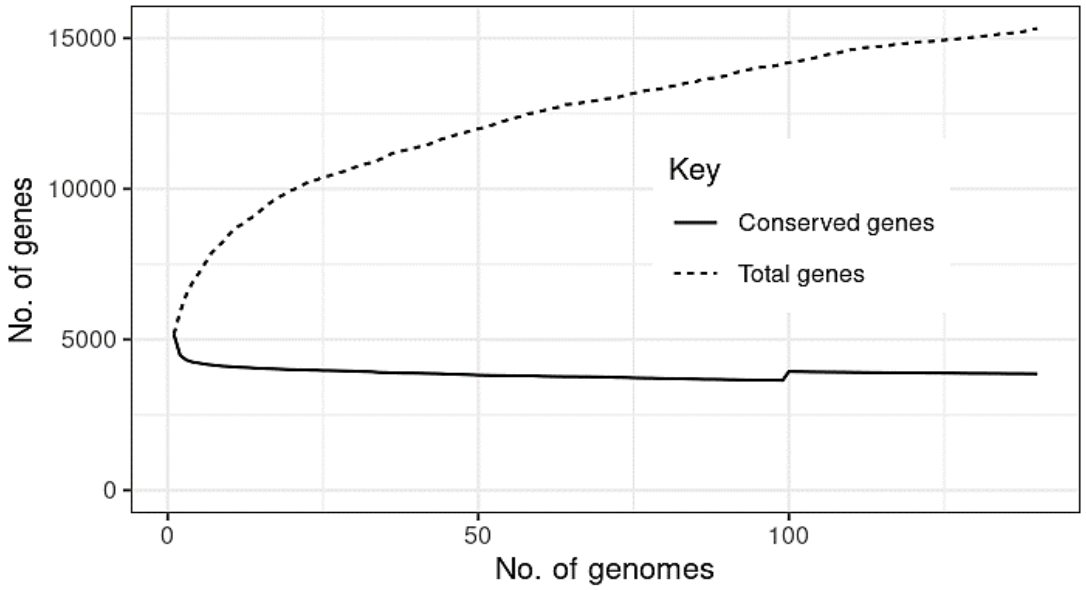

Figure 4. Detail pattern of total genes and conserved genes.

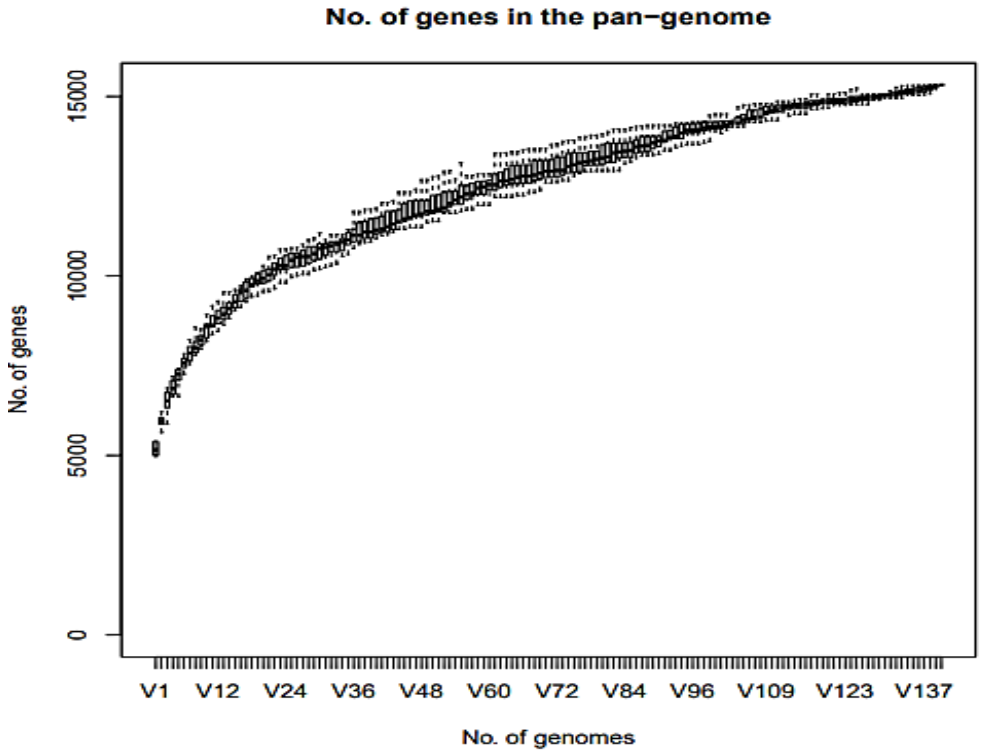

Figure 5. Association among *K. pneumoniae* pan-genes and genomes.

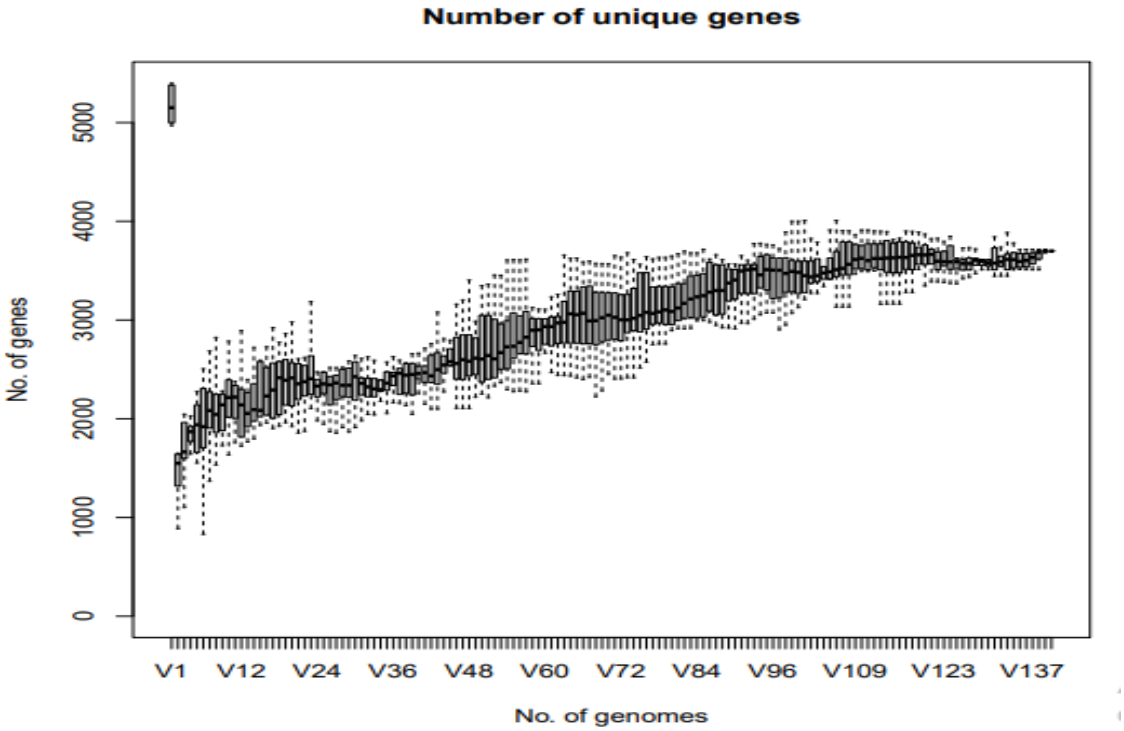

Figure 6. Rising pattern among number of unique genes and number of genomes.

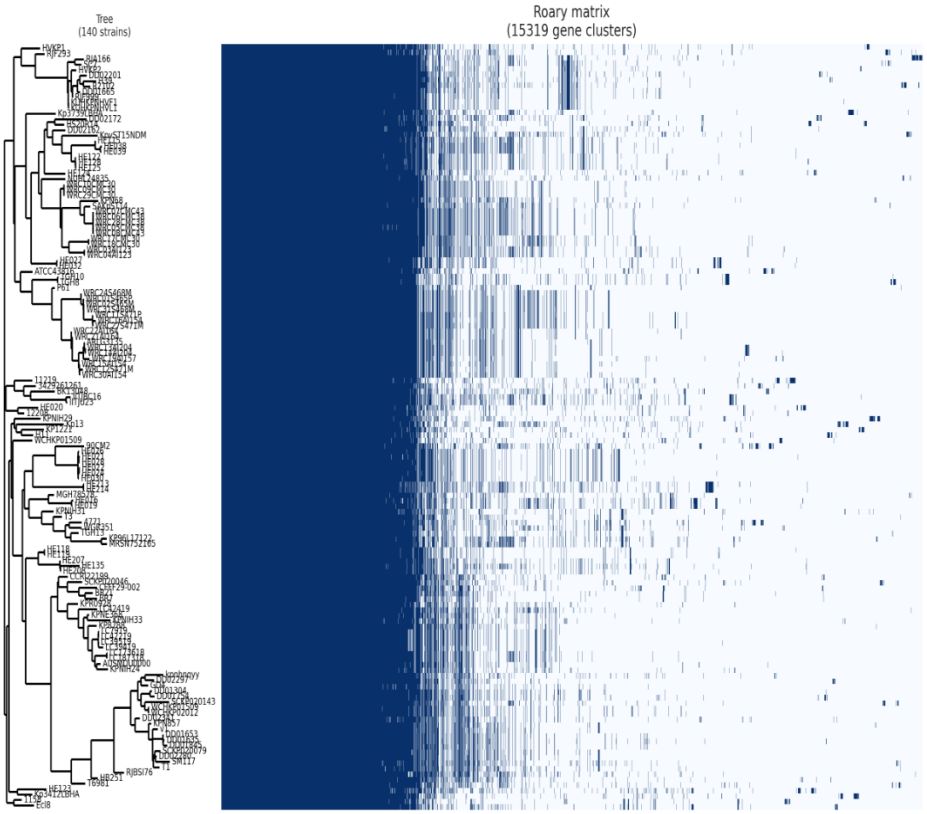

Figure 7. Pan genome tree of core and accessory genes among *K. pneumoniae*

Prioritizing core vaccine targets: Total 128 complete genomes and 12 genomes from draft genomes calculated by pipeline Pan RV was used for prioritizing vaccine candidates. Four independent filtering criteria, 3864 *K. pneumoniae* strains core proteins were applied. The sub-cellular localization prediction is being performed and the result obtained indicate that there are 86 proteins of outer membrane and extra-cellular. Then, the incorporation of DEG in the Pan RV platform predicted 1699 core proteins. The virulent proteins screening was also conducted because identifying the virulent factors is crucial in the development of vaccines and 887 virulent proteins were identified. From the proteomics data it was determined that 2994 proteins were expressing less than 2 trans membrane helices. The RV module jointly identified a total of 8 potential vaccine candidates. All detailed data and the complete list of candidate proteins are provided in Table 1.

Table 1. List of potential vaccine candidates.

Sr. No.	Protein Name	Human Non Homology	Gut Non Homology	Localization	Essential	Virulent	Helics	Mol. Weight (Da)	Annotated
1	oprmC	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	Outer Membrane	1	70	N:0	48216.4651	92.16%
2	ompC	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	Outer Mentrane	2	40	N1	40634.8868	92.16%
3	ompN	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	Outer Membrane	2	40	IN:1	4242.16289	79.17%
4	yedS	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	outer Membrane	2	40	IN:1	39509.614	66.67%
5	oprM	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	Outer Membrane	1	2	OUT:0	49964.4824	34.76% %
6	phoE	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	Outer Membrane	2	40	OUT:0	38723.481	98.86%
7	cusC	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	Outer Membrane	1	71	IN:1	50608.416	75.98%
8	fimD	✓	✓	✓	✓	✓	✓	✓	✓
		0	0	Outer Membrane	3	193	OUT:0	43777.5436	46.00%

These predictions were performed using the online web-based stand-alone tool CELLO2GO. By leveraging the COG (Clusters of Orthologous Groups) database integrated within Pan RV, eight potential vaccine candidates were identified based on their molecular functions. These include FimD/PapC, TolC, and general porin proteins. FimD/PapC is an usher protein located in the outer membrane of bacteria, involved in pilus assembly and bacterial adhesion to host tissues. It is classified under COG category N, which pertains to cell motility and secretion. TolC plays a role in drug efflux and toxin export, falling under COG category V, associated with defense mechanisms. General porins facilitate the passive

diffusion of small molecules across the bacterial outer membrane and are categorized under COG M, related to cell envelope biogenesis—outer membrane. The involvement of these proteins in adhesion, efflux, toxin export, and molecular transport highlights their potential as promising vaccine targets. The detailed biological processes and molecular functions of these proteins are listed in Table 2.

Table 2. Potential vaccine candidates with their biological & molecular functions, location and COG category.

No	COG Category	COG Class	Location	Protein name	Molecular Function
1	COG3188	N	Outer membrane protein	FimD/PapC	Outer membrane usher protein involved in pilus assembly and bacterial adhesion
2	COG1538	M	Outer membrane protein	TolC	Outer membrane protein involved in drug efflux and toxin export
3	COG3203	M	Outer membrane protein	(porin)	Outer membrane proteins that facilitate the passive diffusion of small molecules
4	COG3203	M	Outer membrane protein	(porin)	Outer membrane proteins that facilitate the passive diffusion of small molecules
5	COG1538	M	Outer membrane protein	TolC	Outer membrane protein involved in drug efflux and toxin export
6	COG3203	M	Outer membrane protein	(porin)	Outer membrane proteins that facilitate the passive diffusion of small molecules
7	COG3203	M	Outer membrane protein	(porin)	Outer membrane proteins that facilitate the passive diffusion of small molecules
8	COG1538	M	Outer membrane protein	TolC	Outer membrane protein involved in drug efflux and toxin export

Epitope prioritization: Following the prediction of allergenicity, antigenicity, and toxicity, a total of 33 MHC class I candidates and 14 MHC class II candidates were identified as antigenic, non-allergenic, and non-toxic. The detailed information for these candidates is provided in Table 3, and their 3D structures are illustrated in Figures 8 and 9. An epitope, also known as an antigenic determinant, is the specific part of an antigen recognized by the immune system. Based on IEDB analysis, a total of 4 B-cell epitopes and 38 MHC I-derived epitopes were identified. These epitopes are listed in the table below and were further prioritized for vaccine development (Table 3). Additionally, 18 MHC II epitopes were predicted from IEDB, and their details are provided in the subsequent table. These epitopes underwent a prioritization process to identify the most suitable vaccine candidates (Table 4).

Table 3. B cell epitopes with predicted MHC class I epitopes

No.	B CELL	MHC1	Alleles	Start	End	Length
1	KEMLPDSLHGFA	EMLPDSLHG	27	2	10	9
		EMLPDSLHGF	27	2	11	10
		KEMLPDSLH	27	1	9	9
		KEMLPDSLHG	27	1	10	10
		LPDSLHGFA	27	4	12	9
		MLPDSLHGF	27	3	11	9

		MLPDSLHGFA	27	3	12	10
		EINDLYATG	27	2	10	9
		EINDLYATGS	27	2	11	10
		FEINDLYAT	27	1	9	9
2	FEINDLYATGSA	FEINDLYATG	27	1	10	10
		INDLYATGS	27	3	11	9
		INDLYATGSA	27	3	12	10
		NDLYATGSA	27	4	12	9
		AILQREGQL	27	2	10	9
		AILQREGQLD	27	2	11	10
3	LAILQREGQLD	ILQREGQLD	27	3	11	9
		LAILQREGQ	27	1	9	9
		LAILQREGQL	27	1	10	10
		CCTQSGRTK	27	13	21	9
		CCTQSGRTKG	27	13	22	10
		CTQSGRTKG	27	14	22	9
		CTQSGRTKGR	27	14	23	10
		DCCTQSGRT	27	12	20	9
		DCCTQSGRTK	27	12	21	10
		DFVDNSSTQ	27	2	10	9
		DFVDNSSTQR	27	2	11	10
		DNSSTQRDC	27	5	13	9
		DNSSTQRDCC	27	5	14	10
		FVDNSSTQR	27	3	11	9
		FVDNSSTQRD	27	3	12	10
		NSSTQRDCC	27	6	14	9
4	QDFVDNSSTQRDCCTQSGRTKGR	NSSTQRDCCT	27	6	15	10
		QDFVDNSST	27	1	9	9
		QDFVDNSSTQ	27	1	10	10
		QRDCCTQSG	27	10	18	9
		QRDCCTQSGR	27	10	19	10
		RDCCTQSGR	27	11	19	9
		RDCCTQSGRT	27	11	20	10
		SSTQRDCCT	27	7	15	9
		STQRDCCTQ	27	8	16	9
		STQRDCCTQS	27	8	17	10
		TQRDCCTQS	27	9	17	9
		TQRDCCTQSG	27	9	18	10
		TQSGRTKGR	27	15	23	9
		VDNSSTQRD	27	4	12	9
		VDNSSTQRDC	27	3	11	9

Table 4. B cell epitopes with predicted MHC class II epitopes

No.	B CELL	MHC II	Alleles	Start	End	Length
1	KEMLPDSLHGFA	EMLPDSLHGFA	27	2	12	11
		KEMLPDSLHGF	27	1	11	11
2	FEINDLYATGSA	EINDLYATGSA	27	2	12	11
		FEINDLYATGS	27	1	11	11
3	LAILQREGQLD	LAILQREGQLD	27	1	11	11
	QDFVDNSSTQRDCCTQSGRTKGR	CCTQSGRTKGR	27	13	23	11
		DCCTQSGRTKG	27	12	22	11
		DFVDNSSTQRD	27	2	12	11
		DNSSTQRDCCT	27	5	15	11
		FVDNSSTQRDC	27	3	13	11
		NSSTQRDCCTQ	27	6	16	11

	QDFVDNSSTQR	27	1	11	11
	QRDCCTQSGRT	27	10	20	11
	RDCCTQSGRTK	27	11	21	11
	SSTQRDCCTQS	27	7	17	11
	STQRDCCTQSG	27	8	18	11
	TQRDCCTQSGR	27	9	19	11
	VDNSSTQRDCC	27	4	14	11

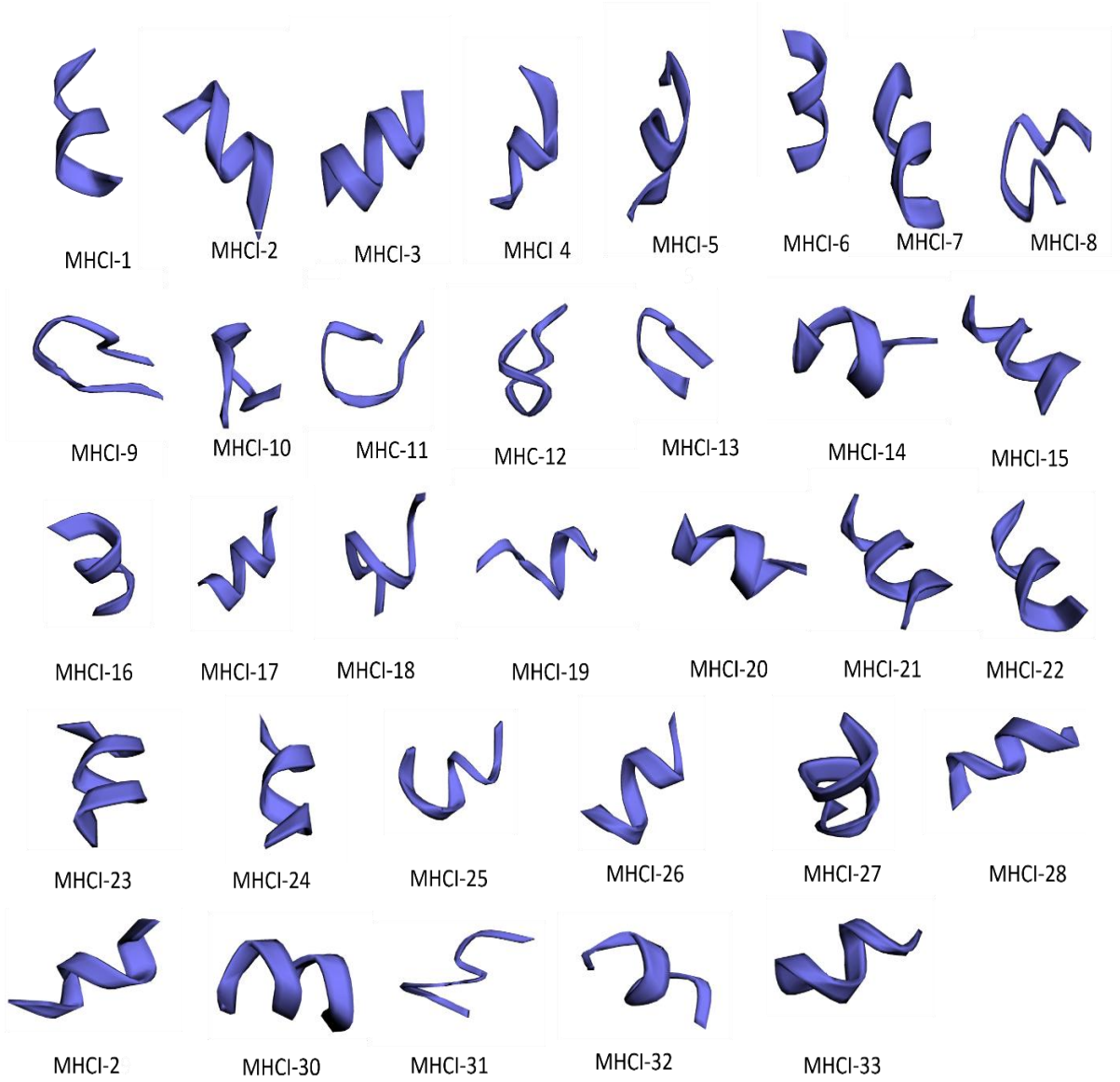

Figure 8. 3D structures of MHC I.

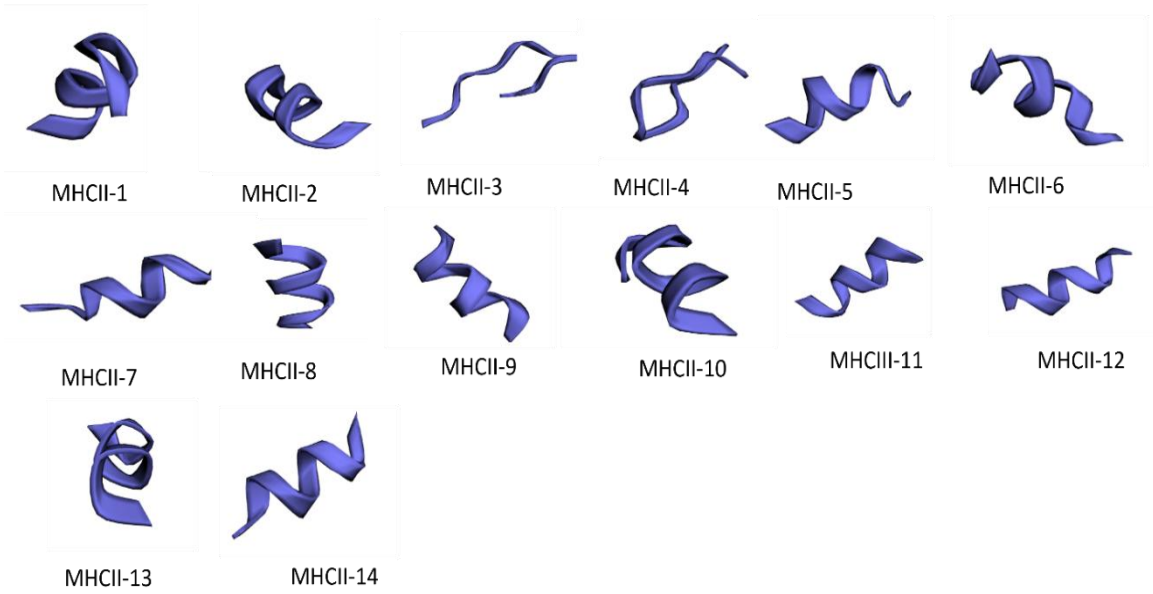

Figure 9. 3D structures of MHC II.

DISCUSSION

The overuse and misuse of antibiotics in the treatment of infectious diseases have serious consequences for both public health and socio-economic development, primarily by accelerating the emergence and spread of antimicrobial resistance among pathogenic bacteria. The increasing prevalence of antibiotic-resistant bacterial strains has reduced the effectiveness of commonly used antimicrobial agents (Khan *et al.,* 2022). This comprehensive study explores innovative strategies to develop effective vaccines against *K. pneumoniae*, especially given the current lack of approved vaccines and challenges such as reactogenicity, short protection duration, and instability of potential candidates. Furthermore, it has been noted that all potential *K. pneumoniae* vaccinations are limited by reactogenicity, a short protection duration, and instability (Lin *et al.,* 2022).

In this study, pan genomics and reverse vaccination techniques were used to analyze 140 fully sequenced genomes. The proteomic comparison of genomes revealed that the pan-genome is still open and can be closed with the addition of a few more genomes. It also highlighted the gain and loss of genes during evolution and their pathogenic persistence in human hosts (Giovanetti *et al.,* 2020). Most pan genomes comprise of unique genes obtained via horizontal gene transfer and the rest contain core genes This indicates that the pathogen possesses a significant ability to acquire and lose genes to live in varying environments and cause infections (Olatunji *et al.,* 2024; Kot, 2019). By focusing on the core genome, the study identified eight promising vaccine candidate proteins based on criteria such as subcellular localization, immunogenicity, and conservation. Consequently, we have used the core genome to assess possible potential vaccine candidates. Among the 140 strains' 3864 core genes, 8 protein possibilities fulfilled all of the chosen requirements in the RV module. Eight of these PVCs were chosen as their subcellular location makes them attractive candidates for vaccination. Of these eight proteins, three TolC proteins involved in the drug efflux and toxin export, four Porin proteins involved in facilitate the passive diffusion of small molecules, one FimD/ PapC outer membrane protein involved in pilus assembly and bacterial adhesion. Bacterial adaptation appears to be mostly dependent on the plasticity of outer membrane porin expression, which may also be crucial for persisted cells under antibiotic treatment (Bialek-Davenet *et al.,* 2017). Outer membrane protein (OMP) considered very important for transport of molecules, maintains of membrane integrity and pathogenesis because these OMP have conserved amino acid sequence (Alzarea, 2022).

Among all those epitopes, MHC I and II from the chosen PVCs were ranked according to their allele count, immunogenicity, viability and antigenicity. It is believed that they elicit humoral and cell-mediated immunological responses, respectively (Hakimian *et al.,* 2024). This study underscores the importance of leveraging genomic data and reverse vaccinology to identify stable, immunogenic targets in *K. pneumoniae*. Such approaches can accelerate the development of vaccines capable of providing durable immunity, ultimately aiding in the fight against multidrug-resistant infections. The genomics revolution has transformed vaccine discovery by enabling the identification of novel therapeutic and prophylactic vaccine candidates through next-generation sequencing and advanced bioinformatics approaches. One of the most influential strategies emerging from this advancement is reverse vaccinology, which facilitates the systematic

identification of potential vaccine antigens directly from pathogen genome sequences without the need for conventional microbial culture. By prioritizing surface-exposed, secreted, and highly conserved proteins with immunogenic potential, RV has accelerated the development of effective vaccine candidates against numerous infectious pathogens (Mushtaq *et al.,* 2022).

Conclusions: *K. pneumoniae* has emerged as a major public health threat, especially due to the rise of community-acquired infections and multidrug-resistant strains. Traditionally considered an opportunistic pathogen, it is now among the top pathogens worldwide. Various approaches have been investigated to prevent its infections. These methods have some limitations such as the higher reactogenicity of whole cell vaccines or the poorer immunogenicity of sub-unit formulations. An integrated analytical approach combining reverse vaccinology with pan-genome analysis has been employed. We identified 47 antigenic epitopes and narrows down to 8 potential vaccine candidate proteins. These candidate proteins are strongly associated with bacterial virulence and survival. Further experimental studies are needed to evaluate their immunogenicity and protective efficacy.

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