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Project Report of 2025: SVP-2524

"Recent Developments in Carbohydrate-Drug Conjugates Vaccines in Antimicrobial Resistant Pathogens"

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SRIVIPRA PROJECT 2025

Title : Recent Developments in Carbohydrate-Drug Conjugates Vaccines in Antimicrobial Resistant Pathogens

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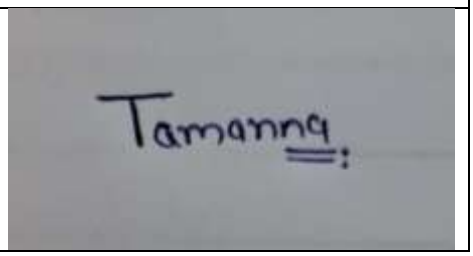
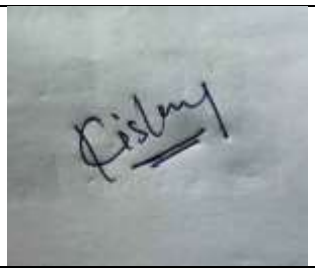
3.		Tamanna	1524048	B.Sc. (H) Chemistry, Semester III	

4.		Kislay	1224051	B.Sc. (H) Biochemistry, Semester III		

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Signature of Mentors

Certificate of Originality

This is to certify that the aforementioned students from Sri Venkateswara College have participated in the summer project SVP-2524 titled **"Recent Developments in Carbohydrate-Drug Conjugates Vaccines in Antimicrobial Resistant Pathogens".** The participants have carried out the research project work under our guidance and supervision from 1st July, 2025 to 30th September, 2025. The work carried out is original and carried out in a hybrid mode.

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Signature of Mentors

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Objectives

The main objective of this project is to inculcate scientific aptitude and research skills in the students by simultaneously providing knowledge and awareness about the role of carbohydrate-based drug conjugates in antimicrobial disease.

Introduction

Antimicrobial resistant (AMR) is a major global health threat, linked to nearly 5 million deaths in 2019– surpassing HIV and malaria. It results from natural bacterial mechanisms, worsened by antibiotic misuse, and is especially severe in sub-Saharan Africa and South Asia [1]. AMR compromise surgeries, transplant, cancer therapies and chronic disease management [2]. High – priority pathogens, including the FSKAPE group (E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa and Enterobacteriaceae), pose the greatest concern [3] (Figure 1).

Vaccination is a key strategy to reduce antibiotic use and slow resistance [4]. Existing vaccines against S. pneumoniae, H. influenzae type b, S. typhi, influenze, and others already help limit AMR, while veterinary vaccines could give antibiotic use in farming. Carbohydrates-based glycoconjugate vaccines, developed by linking bacterial polysaccharides to proteins, have proven for most major AMR pathogens, particularly ESKAPE bacterial remain an urgent unmet need [5].

Bacterial surfaces are coated with polysaccharides (PS) such as lipopolysaccharide, teichoic acids, peptidoglycans, and capsular polysaccharides, which promote biofilm formation, virulence and immune evasion [6]. Vaccines made from plain polysaccharides have shown limited effectiveness because these antigens trigger only T cell- independent immune responses. They mainly induce short -lived IgM and IgG2 antibodies without generating long – term immune memory, and they are ineffective in young children and elderly individuals with immature or weakened B cell responses [7]. Repeated administration can even lead to hypo responsiveness.

To overcome these limitations, polysaccharides are coupled to carrier proteins to create glycoconjugate vaccines. These stimulate a T cell- dependent cell immune response, enabling affinity maturation, class switching to IgG, and the formation of long-lasting memory B and T cells, resulting in strong protection. Recent studies have also identified carbohydrate specific T helper cells (Tcarb cells), which recognise

glycan- peptide fragments presented on MHCII molecules [8] (Figure 2.). This mechanism highlights the complexity of anti-carbohydrate immune responses and suggests new opportunities for designing more effective glycoconjugate vaccines [9].

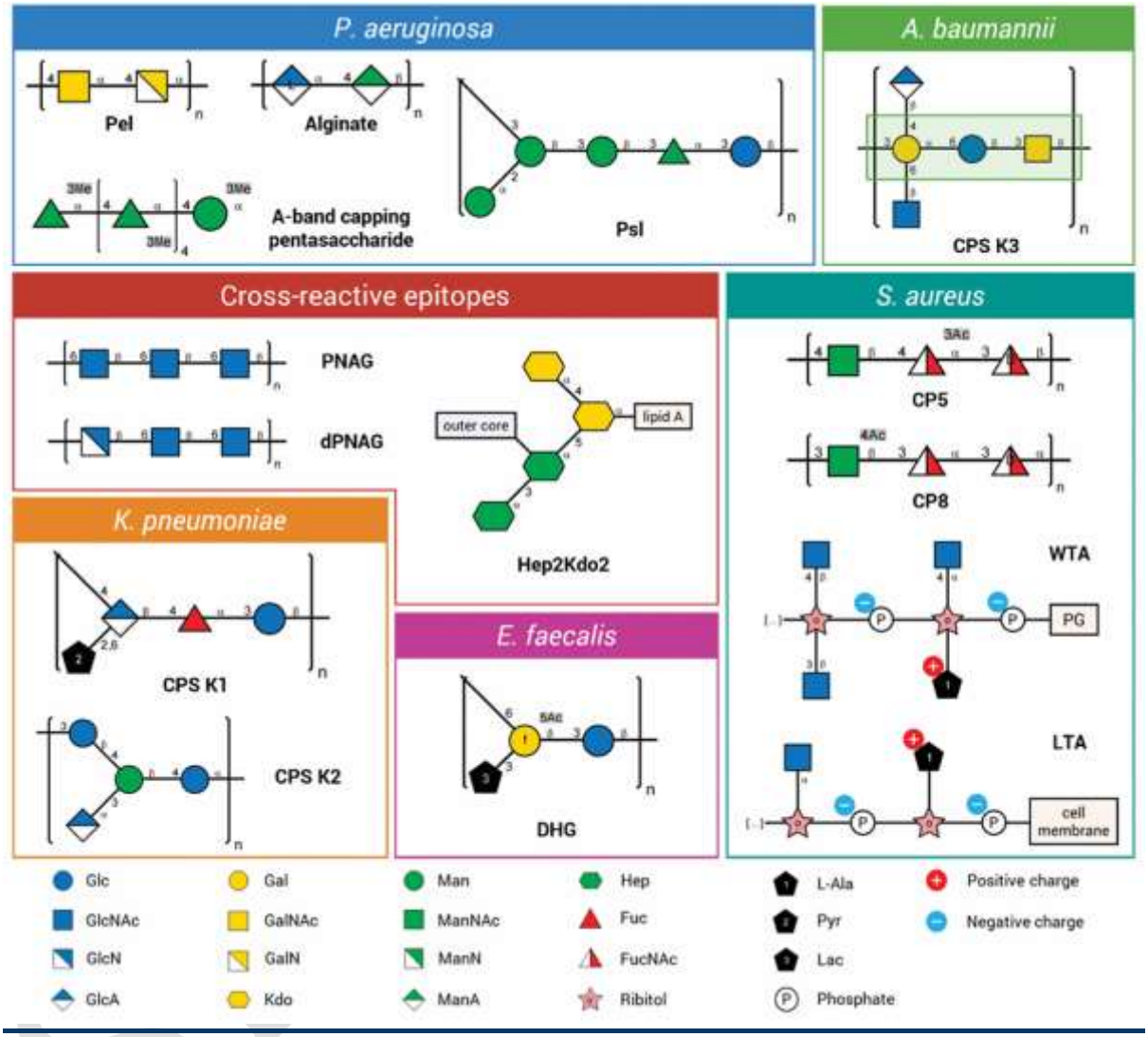

Figure 1. The structural diversity of surface polysaccharides across ESKAPE pathogens is highlighted.

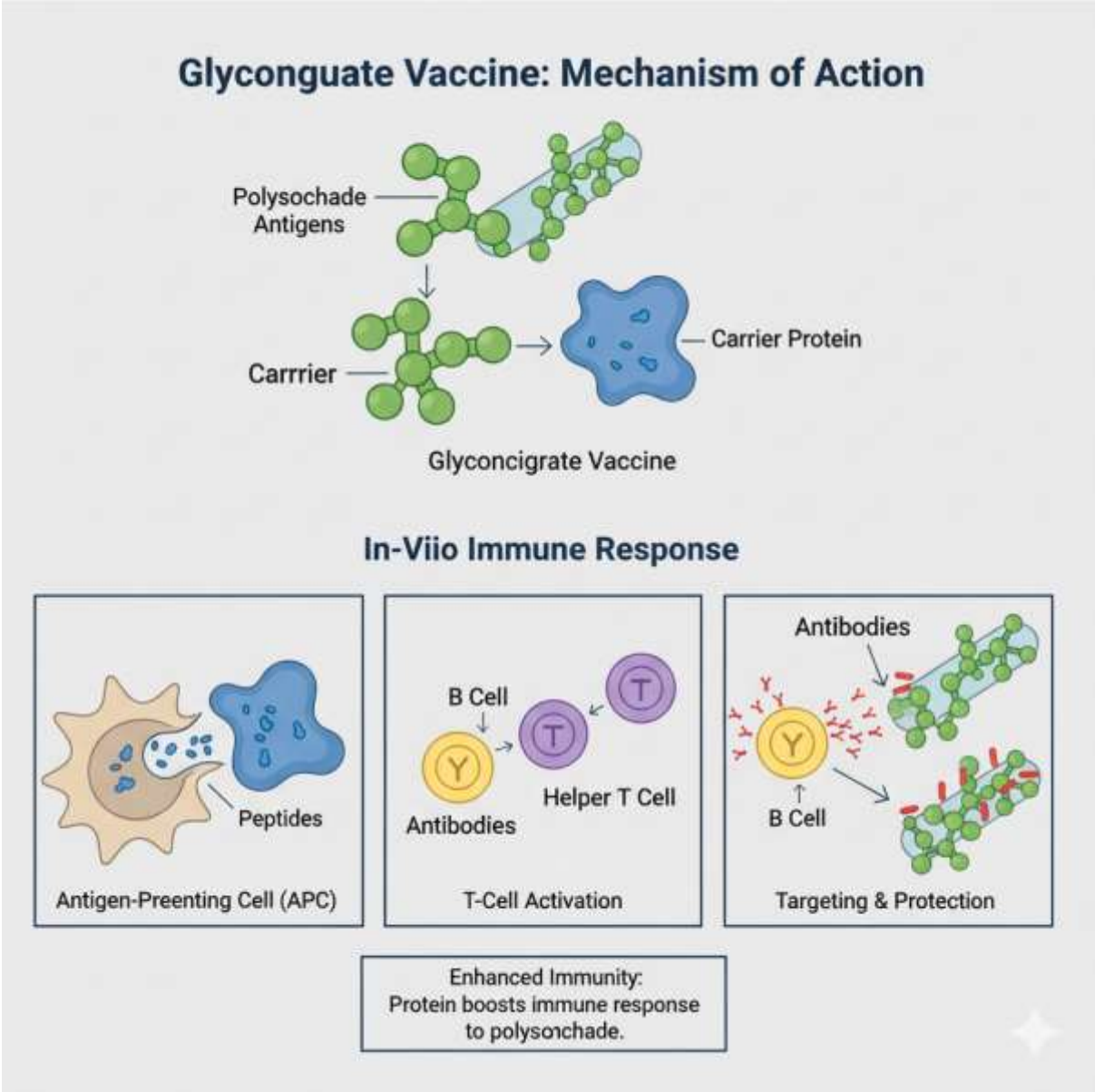

Figure 2. Mechanism of Glycoconjugate Vaccine

Carbohydrates-Based Vaccines Technology

A. Glycan Antigen Production

Licensed glycoconjugate vaccines are usually made by chemically linking bacterial polysaccharides (PS) to carrier proteins, but this process often produces large, heterogeneous structures [10]. To improve consistency, defined oligosaccharides with lower molecular weight are increasingly favoured [11]. Advances in organic synthesis and chemoenzymatic methods now allow the production of highly pure, well- characterized glycans, free from bacterial contaminants [12]. Several

synthetic vaccines, such as a H. influenzae type b vaccine licensed in Cuba, a PNAG conjugate (Phase I), and a Shigella vaccine (Phase II) [13] highlight the progress of this approach, through multivalent vaccine manufacturing synthesis offers an eco- friendly alternative with precise oligosaccharide production, but limitations include access to rare sugar building block [14]. To date, no chemoenzymatic glycoconjugate vaccine has advanced to clinical trials.

B. Approaches of Glycoconjugate Vaccine

Traditional glycoconjugate vaccines often rely on random polysaccharide–protein coupling, which produces heterogeneous structures with variable antigen loading. More defined approaches use oligosaccharides conjugated at the reducing end or via spacers and advanced site-selective strategies employ unnatural amino acids (uAA) or in vivo protein – glycan coupling technology (PGCT) uAA-based methods have enabled the development of multivalent vaccines, including a 24- valent pneumococcal vaccine now in Phase II trials [15]. PGCT, which uses bacterial glycosylation machinery to generate bioconjugates directly in E. coli, has Shigella, E. coli, S. pneumoniae and K. pneumoniae, several of which have advanced to Phase I- III clinical studies [16]. While these technologies improve control and scalability, the limited saccharide loading capacity may be a challenge for weakly immunogenic polysaccharides, requiring further clinical validation.

C. Nanotechnologies for Glycoconjugates Vaccines

Nanotechnologies are emerging as powerful tools to enhance glycoconjugate vaccine design by improving antigen presentation and immune response. Self-assembling nanoparticles (NP), including virus-like particles (VLP), can display polysaccharides in highly ordered, multivalent structures that mimic pathogens and promote strong B cell activation [17]. VLP – based carriers have already been used successfully in licensed vaccines (e.g. HBV, HPV) and recent studies shows their potential as carbohydrates carriers against S. pneumoniae, meningococcal group C and V. cholerae.

Generalized modules for membrane antigens (GMMA) derived from engineered Gram-negative bacterial outer membrane vesicles, naturally present polysaccharides and pathogen-associated molecular patterns, providing properties GMMA-based. Vaccines have shown safety in clinical trials

and promising immunogenicity in preclinical models against pathogens such as Shigella, Neisseria meningitidis, S. Typhi, and S. aureus [18].

The multiple antigens presenting system (MAPS) presenting another innovative approach, assembling protein and polysaccharide antigens through affinity binding rather than covalent linkage. This strategy mimics the complexity of whole -cell vaccines and can induce both humoral and Th1/Th17- biased responses. MAPS has already advanced to Phase II clinical trials with a 24-valent pneumococcal vaccine and is being explored for multivalent vaccines against K. pneumonia and P. aeruginosa [19].

Vaccine Developments Against Capsular Polysaccharides

A. Acinetobacter baumannii

A. Baumannii includes more than 90 capsular polysaccharide (CPS) serotypes in which about 20 have been structurally characterized so far. CPS are widely studied as vaccine antigens due to its presence on the surface of the bacteria which makes it accessible to the host immune system. Studies with monoclonal antibodies (mAbs) against the K1 CPS serotype shows their functional potential, as these antibodies were able to bind 13 out of 100 clinical isolates which promote neutrophil-mediated killing in vitro, and significantly reduce bacterial burden across multiple organs in infected rat [20].

Further studies highlighted the CPS of strain SK44 as another promising candidate. Antibodies raised against SK44 CPS responded to 62% of 554 tested isolates, which suggests that this serotype could provide broader protection against circulating A. baumannii strains. K3 CPS type is structurally characterized by a branched pentasaccharide containing a conserved trisaccharide repeating unit, is also shared with other strains e.g. SK44. This structural conservation may explain its observed cross-reactivity and has spurred interest in its use for vaccine design. Furthermore, conjugating K3 CPS with cholera toxin B subunit produced a bioconjugate capable of providing significant production [21].

More recently, glycoconjugate based on K9 CPS fragments coupled to carrier proteins such as bovine serum albumin (BSA), ovalbumin (OVA), and keyhole limpet hemocyanin (KLH) enhanced immunogenicity and improved survival in mice. Other than CPS, several O-antigen structures of A.

baumannii have been identified, but their diversity and incomplete understanding of prevalent forms in clinical isolates remain a challenge for developing OPS-based vaccines [22].

B. E. coli

Around 80 types of capsular polysaccharides (CPS) have been identified in E. coli so far. Studies suggest that urinary tract infections (UTIs) and bloodstream infections is caused mainly by 10 serotypes. That is the reason why vaccines are mainly targeting these O-antigens. ExPEC$V vaccine includes O-antigen from four serotypes (O1A, O2, O6A, O25B) linked to Pseudomonas exotoxin A (EPA). It triggered the immune response in phase II trials and was safe to use too, but its coverage was limited to 30-35% of serotypes [23]. To improve this, a 10-valent vaccine (ExPEC10V) and a combination of nine bioconjugates (ExPEC9V) were developed for phase iii trials, aiming to prevent infections in older adults with recurrent UTIs.

Some of the serotypes e.g. O25A and O25B, are not much efficient in stimulating immune response, which is a problem because O25B is a major cause of drug-resistant infections. Changing the glycan structure in O25B conjugates immune response in mice and protected them from deadly infections. Similar strategies with chemically synthesized O25B sugars also worked well [24]. For Enterotoxigenic Escherichia coli, bioconjugate vaccines against O148 and O78 were developed using non-pathogenic E. coli extracts. These vaccines triggered antibodies that killed bacteria and reduced gut colonization in mice, showing they can protect mucosal surfaces [Williams AJ, Warfel KF, Desai P, et al. A low-cost recombinant glycoconjugate vaccine confers immunogenicity and protection against enterotoxigenic Escherichia coli infections in mice.

C. Enterococcus Faecalis and Enterococcus faecium

After the discovery of an LTA(lipoteichoic acid)-like structure which was composed of α-Glc-(1,2)-α-Glc-(1,2)-glycerol-3-phosphate. Since then, several different classes of polysaccharides have been isolated from E. Faecalis. Analysis of the CPS biosynthetic locus has defined four serotypes (A-D). Studies of clinical isolates indicated that most pathogenic strains belong to serotype C, although other investigations suggested that the diversity of serotypes is broader 168. Early studies showed that purified CPS reduced the opsonophagocytic killing (OPK) activity of immune rabbit sera while inducing strong antibody titers capable of mediating bacterial OPK [25].

Recently, diheteroglycan (DHG) was identified as an immunogenic component of CPS-C and CPS-D, making it a promising target for antibodies with OPK activity. An opsonic monoclonal antibody against DHG was isolated and demonstrated protective efficacy in passive immunotherapy. In addition, glycoconjugates consisting of DHG linked to SagA ot PpiC proteins proved effective as vaccines against several Enterococcus species, with this E. faecium proteins functioning both as carrier and antigen. Ongoing studies aim to refine glycoconjugate design to achieve maximum immunogenicity while ensuring controlled production. Along these lines, synthetic oligomers mimicking DHC from E. faecalis type 2, conjugated to BSA have been evaluated in mice. Notably anti-DHG antibodies were also able to recognize cell wall antigens of E faecium strain U0317 [26].

In contrast, much less is known about CPS in E. faecium. although bioinformatic predictions have identified putative CPS biosynthetic genes, most structural studies have instead described teichoic acid. Kodali et al. isolated four extra cellular polysaccharides from E. faecium and conjugated them to CRM 197 for rabbit immunization. Of these, the Pf2-CRM197 conjugate, which contained heteroglycans with alturonic acid, showed the greatest effectiveness. Antibodies raised against this conjugate had a strong OPK activity and significantly lowered bacterial counts in liver and kidneys of mice. alturonic acid, a derivative of glucuronic acid, is rare carbohydrate also found in the CPS or LPS of other pathogens, and therefore represents a potential component for inclusion in multivalent fraction format formulation.

D. Klebsiella pneumoniae

Klebsiella pneumoniae is a Gram-negative rod that has emerged as a major threat in modern hospital settings. On the one hand, it is a normal resident of the human gut, but several strains have evolved into highly pathogenic forms, causing severe hospital-acquired infections such as pneumonia, sepsis, and complicated urinary tract infections. Two main features make this pathogen successful: its thick polysaccharide capsule and its alarming ability to develop carbapenem resistance [27].

The capsule functions like a protective wall, preventing host immune cells, such as phagocytes, from engulfing and killing the bacterium. This capsule has been the prime target for vaccine development, but the challenge lies in its diversity, more than 79 different K-antigen types exist. Consequently, the protective range of a single vaccine remains limited [28].

The more pressing concern is the growing resistance to antibiotics. K. pneumoniae has become a "carbapenemase factory," producing enzymes like NDM and KPC that deactivate carbapenem antibiotics, often considered the last line of defense against multidrug-resistant infections [10.3390/ijms22084042]. The genetic determinants of these enzymes are typically carried on mobile plasmids, allowing for rapid horizontal transfer across bacterial species. This has accelerated the global spread of resistance, making K. pneumoniae one of the gravest public health threats. The lack of a global vaccine and the rising inefficacy of antibiotics underscore the urgent need for alternative prevention strategies [29].

E. Pseudomonas aeruginosa

Pseudomonas aeruginosa is a highly versatile and opportunistic Gram-negative bacillus, notorious for causing infections in immunocompromised individuals such as burn victims, ventilated ICU patients, and those with cystic fibrosis. One of its major survival strategies is forming biofilms, complex communities of polysaccharides and proteins that protect the bacteria from antibiotics and immune responses [30].

Biofilms not only impede antibiotic penetration but also facilitate persistence of infection, leading often to chronic and difficult-to-treat disease. Moreover, P. aeruginosa carries a wide set of virulence factors lipopolysaccharides, flagellum, outer membrane proteins, secretion systems, and more that contribute to its pathogenicity and evoke strong immune evasion.

Recent vaccine development has explored multicomponent formulations designed to elicit both functional antibodies and T-helper responses such as Th17, which are shown in mice to confer enhanced protection against acute pneumonia. Nano-emulsion based subunit vaccines are also emerging, aiming for broad antigen coverage and better immune stimulation. Despite decades of work and several clinical trials (e.g. IC43), no vaccine has yet obtained regulatory approval, which reflects the challenge of antigenic variability and immune evasion [31].

F. Staphylococcus aureus

Staphylococcus aureus is a Gram-positive bacterium and a major public health challenge, often residing harmlessly in the skin and nasal passages of healthy people but capable of causing severe infections when it breaches barriers or immunity weakens. Approximately one-third of the population

are carriers, often asymptomatic, but S. aureus can produce a variety of major diseases including skin infections, pneumonia, bacteremia, endocarditis, and toxic shock syndrome.

Methicillin-resistant S. aureus (MRSA) is of particular concern; it possesses genes such as mecA that confer resistance to methicillin and many other β-lactam antibiotics, complicating treatment. Vaccine development strategies have shifted toward multivalent vaccines combining capsular polysaccharides (especially serotypes CP5 and CP8) and multiple protein antigens, since single antigen vaccines have repeatedly failed in late-phase trials.

Experimental vaccines targeting virulence factors (toxins, cell surface proteins, enzymes) have shown good protection in animal models. For example, a multicomponent vaccine "Sta-V5" composed of five conserved antigens gave near-complete protection across multiple S. aureus disease models in mice. Also, studies in non-human primates with SA4Ag (capsular polysaccharides + protein antigens) demonstrated strong antibody and memory B-cell responses. Despite this progress, no human vaccine has yet reached licensure. Challenges remain: waning immunity over time, antigenic variation, immune evasion via multiple virulence factors, and possible limitations of animal models to predict human efficacy [32].

Pathogen	**Type**	**Virulence & Key Threat**	**Vaccine Status**
Klebsiella pneumoniae	Gram-negative rod	Its capsule prevents immune attack, and it produces carbapenemase enzymes that cause extreme antibiotic resistance.	No licensed vaccine. Research is targeting its capsule.
Pseudomonas aeruginosa	Gram-negative rod	Forms biofilms, which act as a shield against antibiotics, and has many toxins. Often pan-drug resistant.	No licensed vaccine. Development is challenging due to complex virulence.
Staphylococcus aureus	Gram-positive cocci	Capsule and toxins cause severe disease. The rise of MRSA has made it a major threat.	No licensed vaccine. Trials have failed, suggesting a single-target approach is not enough.
Enterococcus faecium	Gram-positive cocci	It forms biofilms and has acquired vancomycin resistance (VRE), making infections very	No licensed vaccine. Research is ongoing.

		difficult to treat.	
Escherichia coli	Gram-negative rod	Pathogenic strains (ExPEC) use adhesins and toxins to cause disease. They are increasingly resistant to common antibiotics.	No licensed vaccine. Complexity and diversity of strains make a universal vaccine difficult.
Acinetobacter baumannii	Gram-negative coccobacillus	Its capsule and biofilm formation allow it to survive in hospitals. It is often pan-drug resistant.	No licensed vaccine. Its capsule is a promising target for development.

Conclusion and Future Outlook

Glycoconjugate vaccines are well-established tools for preventing bacterial infections. They have demonstrated the capacity to elicit opsonic or bactericidal antibodies in humans, effectively protecting against invasive diseases such as pneumonia and reducing bacterial carriage. As a result, carbohydrate-based vaccines hold significant potential in addressing infections caused by ESKAPE pathogens—major contributors to antimicrobial resistance (AMR). Beyond traditional approaches, emerging technologies—including chemically synthesized carbohydrates, bioconjugation, glyconanoparticles/GMMA, and MAPS—are driving the development of next-generation, purpose-designed glycoconjugate vaccines.

Antimicrobial resistance (AMR) remains a global health challenge, with ESKAPE pathogens identified as primary drivers. Developing effective vaccine-based prevention strategies requires identifying clinical syndromes suitable for testing. In 2019, lower respiratory tract, bloodstream, and intra-abdominal infections accounted for nearly 80% of AMR-related deaths, with over 400,000 directly attributed to lower respiratory infections. These conditions are often treated with high volumes of antibiotics, accelerating resistance. Hospital-acquired infections (HAIs) such as central line-associated bloodstream infections (CLABSI), ventilator-associated pneumonia, catheter-associated urinary tract infections (CAUTI), and surgical site infections (SSI) are particularly relevant, predominantly caused by *S. aureus*, *E. coli*, *P. aeruginosa*, and *K. pneumoniae*. However, AMR is not limited to nosocomial settings; community-acquired infections like urinary tract infections (UTIs) also contribute significantly, accounting for 150,000 episodes globally and 11% of antibiotic prescriptions.

E. coli bacteremia, often originating from UTIs, further underscores the need for interventions targeting both hospital and community settings.

Carbohydrate-based vaccines offer a promising approach to counteract AMR, yet several challenges must be addressed. HAIs are often polymicrobial, requiring complex multivalent formulations for effective protection. Biofilm formation in infections such as CAUTI or cystic fibrosis complicates treatment and vaccine efficacy, as biofilms hinder both antibiotics and antibody access. Targeting biofilm-associated glycans (e.g., PNAG, Psl) or proteins, and using agents to disrupt biofilms, could improve outcomes. Most existing glycoconjugate vaccines are based on capsular polysaccharides (CPS), but it is still uncertain whether O-polysaccharides (OPS) can serve as reliable targets due to immune evasion. In *E. coli* and *K. pneumoniae*, capsule structures may obscure O-antigen epitopes, reducing antibody binding. Additionally, *P. aeruginosa* LPS-based vaccines have shown inconsistent results, possibly due to non-protective or suppressive antibody responses. For broad targets like PNAG, safety remains a concern due to cross-species presence. The history of failed *S. aureus* vaccine candidates further illustrates the difficulty of inducing protective immunity against AMR pathogens, as they employ diverse immune evasion mechanisms and require novel approaches involving protein antigens and innovative glycoconjugate designs.

Glycoconjugate vaccines often underperform in immunocompromised, elderly, or comorbid populations—groups at higher risk for AMR infections. Despite multiple boosters, these vaccines may still fail to elicit robust or timely immune responses. In this context, new designs incorporating potent adjuvants and enabling single-dose administration are highly desirable, especially in hospital settings and resource-limited regions. A deeper understanding of immunological mechanisms, including carrier-induced epitope suppression (CIES), is also necessary to guide vaccine formulation. CIES, caused by immune interference from repeated exposure to the same protein carriers, may dampen polysaccharide-specific responses in some conjugate vaccines. However, it is not universally observed, and more research is needed to elucidate its impact. Looking ahead, advanced technologies such as MAPS (Multiple Antigen Presenting Systems), nanoparticles (NP), GMMA (Generalized Modules for Membrane Antigens), and glycoengineering platforms are paving the way for multi-antigen and even multi-pathogen vaccines. These tools are currently in clinical evaluation and are expected to play a pivotal role in the next generation of vaccines designed to address the AMR crisis.

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