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REVIEW ARTICLE

Polysaccharide-Based Drug and Vaccine Delivery Systems for Infectious Diseases: Design Principles, Applications, and Translational Challenges

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Abstract: The global burden of infectious disease remains substantial, compounded by antimicrobial resistance and persistent gaps in vaccine stability, immunogenicity, and equitable distribution. Conventional antimicrobial and vaccine formulations are frequently limited by poor aqueous solubility, rapid systemic clearance, chemical instability, and weak mucosal immune activation. Naturally derived polysaccharides including chitosan, alginate, dextran, starch, cellulose, and hyaluronic acid offer a structurally diverse, readily modifiable biomaterial platform for such systems by virtue of their biocompatibility, biodegradability, and, in several cases, intrinsic immunomodulatory activity. This review synthesizes the current literature on polysaccharide-based drug delivery systems for infectious disease control, examining their natural and semi-synthetic sources, key functional attributes (biodegradability, biocompatibility, mucoadhesion), and the chemical modification strategies that fine-tune these properties for site-specific delivery. We evaluate the translational evidence for polysaccharide-based antimicrobial carriers, including chitosan–antibiotic nanoparticles, alginate wound-healing hydrogels, and dextran–antiviral conjugates, and for polysaccharide-based vaccine platforms that act as antigen-protective matrices and intrinsic adjuvants across oral, nasal, and parenteral routes; marketed polysaccharide-conjugate vaccines against *S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, and *S. Typhi* are discussed as clinical proof of concept. Finally, we critically appraise the translational barriers that constrain broader adoption – raw-material heterogeneity, batch-to-batch reproducibility, sterilization- and endotoxin-related quality concerns, and regulatory ambiguity around hybrid nanostructured carriers – and outline the strategic directions, including stimuli-responsive carriers and integration with mRNA and recombinant-antigen technologies, required to accelerate clinical translation.

Keywords: Polysaccharides; drug delivery systems; vaccine delivery; chitosan; alginate; mucoadhesion; antimicrobial resistance.

1. INTRODUCTION

Infectious diseases continue to place a substantial burden on global healthcare systems, and the tools available to prevent and treat them remain imperfect. Conventional antimicrobial and vaccine delivery strategies are frequently constrained by poor bioavailability, physicochemical instability, and

inadequate activation of protective immunity, limitations that together underscore the need for delivery platforms capable of improving therapeutic efficacy and target specificity [1].

The growing complexity of infectious disease management demands therapeutic agents and delivery platforms that jointly optimize efficacy, safety, adaptability, and accessibility.

Systemic antimicrobial administration and traditional vaccination strategies each face well-documented shortcomings. Antimicrobials often exhibit poor aqueous solubility, rapid systemic clearance, premature degradation, and off-target toxicity; achieving therapeutic concentrations under these constraints typically requires higher dosing, which in turn elevates adverse-effect risk and accelerates the emergence of resistance. Vaccines particularly live-attenuated or inactivated formulations depend on uninterrupted cold-chain logistics, often require multiple booster doses, and can show variable immunogenicity across populations. Moreover, intramuscular administration frequently fails to elicit the mucosal immunity required to intercept pathogens at their principal ports of entry: the respiratory, gastrointestinal, and urogenital epithelia [2,3,4,5].

These limitations point to a clear need for delivery systems that circumvent the drawbacks of conventional platforms while responding dynamically to evolving infectious threats. Polysaccharides naturally occurring biopolymers derived from plants, animals, algae, and microorganisms have emerged as promising candidates for next-generation drug and vaccine delivery. Their intrinsic biocompatibility, biodegradability, resistance to digestion by mammalian enzymes, and ease of extraction, combined with broad functional adaptability, render them well suited to biomedical application [6].

A growing body of literature highlights the multifaceted advantages of polysaccharides for delivery applications, including mechanical resilience, favorable bioavailability profiles, and an abundance of functional groups amenable to chemical conjugation [7]. Polysaccharide-based hydrogels in particular combine tunable chemical architecture with minimal intrinsic immunogenicity and structural versatility, enabling the sustained, regulated delivery of diverse cargos small-molecule drugs, proteins, genes, cells, and vaccine antigens. Their natural abundance from renewable sources such as starch, cellulose, chitin/chitosan, alginate, and dextran further provides a sustainable and cost-effective alternative to synthetic polymers [8,9].

In the specific context of vaccine delivery, several polysaccharides among them β -glucans and chitosan possess intrinsic immunomodulatory and adjuvant activity that can enhance immunogenicity and reduce reliance on synthetic adjuvants. Mucoadhesive derivatives such as thiolated alginate and thiolated chitosan prolong residence time at mucosal surfaces and improve antigen uptake, thereby

promoting localized immunity at the very sites where pathogens first establish infection [10,11,12,13].

Polysaccharide-based carriers can be administered via oral, parenteral, and topical/transdermal routes. Oral formulations protect labile therapeutic agents from gastrointestinal degradation and facilitate mucosal absorption; parenteral systems enable sustained systemic delivery and tissue-specific targeting; and topical or transdermal formats offer needle-free, first-pass-independent alternatives that improve patient adherence. Despite this promise, polysaccharide-based systems still face meaningful translational obstacles, including source-to-source structural variability, microbial contamination risk, inconsistent degradation profiles, and a comparatively limited body of clinical validation. A more complete understanding of in vivo release kinetics and material–tissue interactions is needed, and emerging technologies stimuli-responsive hydrogels sensitive to pH, temperature, light, or ultrasound, and 3D-printed polysaccharide-based dressings are progressively expanding the functional scope of these materials [14,15,16].

This review provides a comprehensive appraisal of polysaccharide-mediated delivery systems in the context of infectious disease control. We critically examine the limitations of conventional antimicrobial and vaccine strategies; describe the properties that make polysaccharides suitable delivery materials biocompatibility, biodegradability, functional versatility, mucoadhesion, immunomodulation, and structural adaptability; and survey current advances in nanocarriers, hydrogels, mucoadhesive platforms, and stimuli-responsive constructs. Particular emphasis is placed on the capacity of these systems to protect labile therapeutics, enable controlled release, engage mucosal as well as systemic immunity, and improve patient adherence. We further address translational barriers, drawing on illustrative preclinical and early clinical examples, and outline future directions and regulatory considerations relevant to the broader adoption of these sustainable platforms in global infectious disease management.

Although a number of reviews have addressed polysaccharide-based drug delivery or polysaccharide vaccine adjuvants separately, most treat antimicrobial and vaccine applications as distinct literatures and rarely evaluate the major polysaccharide carriers side-by-side against shared translational endpoints. The present review distinguishes itself from prior polysaccharide-focused reviews in three respects: (i) it unifies antimicrobial and vaccine delivery applications within a single structure–function framework

rather than treating them as separate bodies of work; (ii) it synthesizes the property-level evidence for the principal polysaccharide carriers into an explicit, criterion-based trade-off assessment (Section 3.6) rather than leaving comparative data (Table 4) to stand without interpretation; and (iii) it explicitly links laboratory-stage findings to clinical trial evidence, marketed products, and regulatory and manufacturing constraints (Sections 6 and 7), rather than confining discussion to preclinical proof-of-concept. This integrated, comparative, and translation-oriented approach is intended to give the review an analytical value beyond that of a literature summary.

1.1 Global Burden of Infectious Disease

Infectious diseases continue to pose a major challenge to public health systems worldwide, a burden compounded by the rise of antimicrobial resistance [17] and the continuing need for more effective vaccination strategies. Recent estimates indicate that infectious diseases such as HIV/AIDS,

hepatitis, dengue, and COVID-19 collectively accounted for more than 8.7 million deaths and 259 million disability-adjusted life years (DALYs) in 2021, with the greatest impact concentrated in low- and middle-income countries. This burden is closely tied to socio-demographic determinants, disparities in healthcare access, and the continued emergence of resistant pathogens. Comprehensive analyses from the Global Burden of Disease (GBD) initiative highlight the need for therapeutic platforms that address both treatment efficacy and delivery constraints (Table 1, Fig. 1). Polysaccharide-based drug and vaccine delivery systems offer a promising response to this need: their biocompatibility, structural versatility, and immunomodulatory properties enable targeted, stable, and responsive delivery of therapeutics, particularly in resource-limited settings. As the field matures, integrating these natural polymers into scalable, regulatory-compliant platforms could meaningfully reduce the global infectious disease burden and improve health outcomes across diverse populations [18]

Table 1. Global burden of major infectious diseases and current limitations in drug/vaccine delivery.

Disease	Global Burden (Latest)	Current Delivery Methods	Challenges	Ref.
Tuberculosis	10.8M cases; 1.25M deaths (2023)	Oral antibiotics, injectable second-line drugs, BCG	Extended regimens, poor macrophage targeting, MDR strains; polysaccharides offer sustained release & intracellular delivery	[19]
Malaria	263M cases; 597K deaths (2023)	ACTs, injectable artesunate, RTS,S vaccine	Resistance, cold-chain needs, poor adherence; polysaccharides enable controlled release & mucosal vaccine stability	[20]
HIV/AIDS	40.8M living with HIV; 630K deaths (2024)	Oral ART, long-acting injectables	Adherence fatigue, cold-chain reliance; polysaccharide depots support long-acting, mucosal PrEP, thermostable vaccines	[21]
Influenza	~1B cases/year; 290K-650K deaths	Injectable & intranasal vaccines, oral antivirals	Annual reformulation, weak mucosal immunity; polysaccharides enhance intranasal delivery & IgA response	[22]
COVID-19	Millions of deaths (2020-21)	mRNA/viral-vector vaccines, oral antivirals	Cold-chain logistics, booster fatigue; polysaccharides support mucosal vaccines & single-dose thermostable formats	[23]

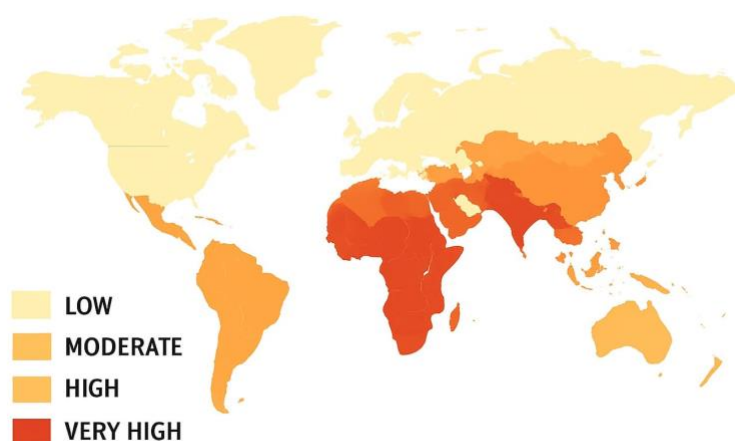


Fig. 1. Global impact and prevalence of leading infectious diseases.

2. METHODS

A systematic literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar to identify recent, high-impact studies on polysaccharide-based drug and vaccine delivery systems for infectious disease control. Search terms included “polysaccharide drug delivery,” “vaccine delivery,” “chitosan,” “alginate,” “dextran,” “cellulose,” “hydrogels,” “mucoadhesion,” “mucosal immunity,” “stimuli-responsive systems,” “antimicrobial resistance,” and “infectious diseases,” used individually and in combination. Priority was given to studies characterizing the physicochemical properties, immunomodulatory potential, and structural versatility of polysaccharides, with particular emphasis on delivery architectures such as nanoparticles, hydrogels, micelles, and scaffolds. The review focused on therapeutic efficacy, mucosal targeting, patient compliance, and translational relevance for the development of sustainable, multifunctional platforms for infectious disease management. As a narrative rather than systematic review, this synthesis does not follow a formal PRISMA protocol; consequently, the conclusions drawn should be interpreted as a critical appraisal of the field rather than a quantitative meta-analysis.

The literature search covered the period from January 2014 to June 2026, with priority given to publications from 2020–2026 to ensure the review reflects recent advances; earlier foundational studies were retained where they established mechanistic or historical context. Records were screened using the following inclusion criteria: (i) peer-reviewed original research or review articles published in English; (ii)

studies reporting polysaccharide-based carriers (natural, semi-synthetic, or chemically modified) applied to antimicrobial or vaccine delivery; and (iii) studies providing physicochemical characterization, in vitro, in vivo, or clinical data relevant to delivery performance. Exclusion criteria were: (i) conference abstracts, preprints without peer review, and non-English-language articles; (ii) studies in which polysaccharides were used solely as excipients unrelated to drug or antigen delivery (e.g., purely nutritional or industrial applications); and (iii) duplicate reports superseded by a later, more complete publication from the same group. Titles and abstracts were first screened for topical relevance, followed by full-text assessment of shortlisted records against the criteria above; reference lists of key reviews were hand-searched to capture additional relevant studies. Of the records identified across the four databases, 149 unique publications met the inclusion criteria and form the evidence base for this review, after removal of duplicate records retrieved from more than one database. As this is a narrative rather than a systematic review, study selection was not independently duplicated by two reviewers, and no formal risk-of-bias scoring was applied; these are acknowledged limitations of the methodology.

3. POLYSACCHARIDES AS BIOMATERIALS FOR DRUG DELIVERY

Polysaccharides are widely regarded as ideal materials for modern drug delivery owing to their natural origin, biodegradability, and biocompatibility. Composed of long carbohydrate chains derived from plants, algae, animals, and microorganisms, they are generally well tolerated by biological systems and are readily modified chemically or

enzymatically for targeted protection and controlled release of therapeutic cargo. Naturally occurring polysaccharides such as chitosan, alginate, hyaluronic acid, cellulose, and dextran are used extensively for their multifunctional properties, including intrinsic gelation, mucoadhesion, and the capacity to form hydrogels, nanoparticles, and covalent conjugates. These features together enable efficient encapsulation and stabilization of therapeutic agents and support tunable release profiles [24].

Polysaccharides can be crosslinked into hydrogels or aerogels, self-assembled into nanoparticles, or chemically conjugated to drugs to form prodrugs responsive to physiological stimuli such as pH or enzymatic activity. This structural versatility underlies the development of “smart” delivery platforms capable of site-specific, controlled, and sustained release, thereby enhancing therapeutic efficacy while minimizing adverse effects [25].

For vaccine applications specifically, polysaccharides offer structurally diverse, biocompatible, and readily modifiable carrier platforms that enhance carrier functionality, protect

labile antigens, improve bioavailability, and enable site-specific targeting. Their origins span natural sources plant, animal, algal, and microbial as well as semi-synthetic derivatives obtained through chemical or enzymatic modification (Fig. 2, Table 2). Identifying the source of a given polysaccharide is critical, since source dictates structural attributes, purity, the profile of available functional groups, and ultimately biomedical applicability [26].

3.1 Sources of Polysaccharides

Natural polysaccharides form the foundational category of pharmaceutically relevant biopolymers. Among marine-derived materials, alginate from brown seaweeds (*Laminaria*, *Ascophyllum*) is valued for its capacity to form gels via ionic crosslinking with calcium ions [27]. This mild gelation chemistry enables the encapsulation of sensitive drugs, vaccine antigens, and even live microorganisms, protecting them en route to their intended site of action. Carrageenan and agar, both derived from red algae, contribute additional gelling and stabilizing properties, although alginate remains the most extensively studied of this group [28].

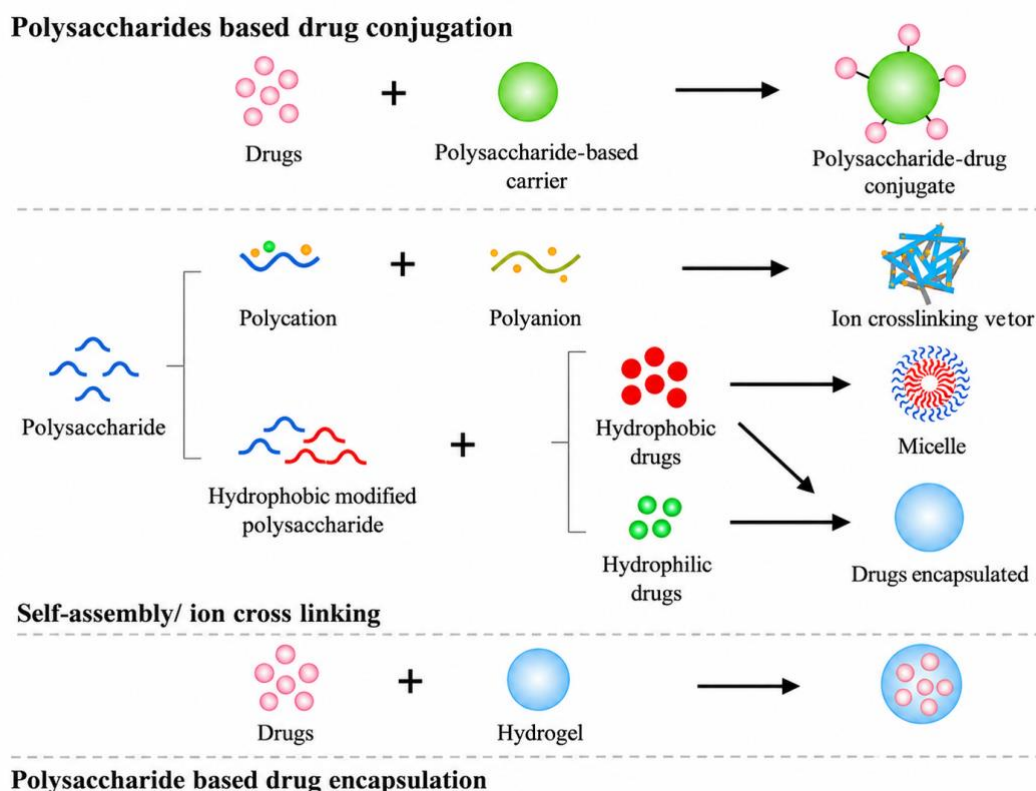


Fig. 2. Schematic representation of polysaccharide-based drug delivery systems, illustrating nanoparticle formation, hydrogel networks, and conjugation strategies for controlled and targeted therapeutic release.

Table 2. Sources and examples of polysaccharides used in drug delivery systems.

Polysaccharide	Source	DDS Properties	Delivery Forms & Applications	Modified Derivatives	Ref.
Chitosan	Crustacean shells, fungal chitin	Cationic, mucoadhesive, permeation enhancer	Nanoparticles, intranasal/oral vaccines, coatings	TMC, thiolated, PEG-chitosan	[29,30]
Alginate	Brown seaweed	Anionic, gel-forming with Ca ²⁺ , biocompatible	Beads/hydrogels, oral/injectable depots	Oxidized, PEG-alginate, grafted forms	[31,32]
Dextran / Ac-Dex	Microbial (Leuconostoc)	Hydrophilic, acid-labile (Ac-Dex)	Nanoparticles, prodrug conjugates, vaccine carriers	Ac-Dex, oxidized, PEG-dextran	[33,34]
Starch	Corn, potato, rice	Enzymatically degradable, low-cost	Oral tablets, gastroretentive hydrogels	Carboxymethyl, grafted, nano-starch	[34,35,36]
Hyaluronic acid	Animal ECM, microbial fermentation	CD44 targeting, viscoelastic, hydrophilic	Injectable hydrogels, tumor-targeted delivery	HAMA, thiolated, PEG-HA	[37,38]
CMC / cellulose	Plant cellulose	Film-forming, mucoadhesive, modifiable	Tablets, hydrogels, wound dressings	CMC, HPMC, methylcellulose	[39]
Pullulan	Microbial (A. pullulans)	Neutral, film-forming, stable	Oral films, nanoparticle coatings	Oxidized, graft copolymers	[40]
Pectin	Fruit peels (apple, citrus)	Anionic, colon-targeting, gel-forming	Colon-targeted beads/hydrogels	Amidated, oxidized, crosslinked	[41]
Carrageenan	Red seaweed	Sulfated, gel-forming, antiviral potential	Topical gels, controlled-release matrices	κ -, ι -, λ -fractions, modified hydrogels	[41,42]
Xanthan gum	Microbial (X. campestris)	Viscous, shear-thinning, stable	Oral sustained-release, hydrogels	Carboxymethyl, grafted forms	[43,44]
Fucoidan	Brown seaweed	Sulfated, bioactive, targeting potential	Nanoparticles, mucosal/antiviral carriers	Oxidized, ligand-conjugated forms	[45]

Among animal-derived polysaccharides, chitosan obtained by deacetylating chitin from crustacean exoskeletons is distinguished by its cationic character and strong mucoadhesive interactions with negatively charged mucosal surfaces, properties that make it particularly advantageous for mucosal vaccine delivery via the nasal or oral routes, where it enhances antigen retention and uptake. Hyaluronic acid (HA), naturally present in connective tissue and synovial fluid, is valued for its biocompatibility, viscoelasticity, and affinity for CD44 receptors on immune and epithelial cells; although traditionally extracted from animal tissue, microbial fermentation now predominates as a production route owing to its improved safety and reproducibility [46].

Plant-derived polysaccharides are widely used because of their availability, biodegradability, and cost-effectiveness.

Starch, sourced from maize, potato, and rice, is enzymatically degraded within the gastrointestinal tract, making it suitable for oral and colon-targeted delivery, though native starch typically requires modification to improve solubility and stability. Cellulose, another abundant plant polysaccharide, is insoluble in its native form but yields water-soluble derivatives carboxymethylcellulose, hydroxypropyl methylcellulose, and microcrystalline cellulose that are well suited to oral tablets, hydrogels, and film-coated carriers [47,48].

Microbial polysaccharides such as dextran, produced by *Leuconostoc mesenteroides*, are notable for their water solubility and their capacity to form stable complexes with proteins and drugs; dextran is widely applied in nanoparticle, hydrogel, and conjugate formulations, with its

biodegradability ensuring safe clearance in vivo. Microbial fermentation also supports high-purity production of hyaluronic acid, eliminating the sterility and immunogenicity concerns historically associated with animal-derived material.

To further enhance solubility, stability, responsiveness, and targeting, semi-synthetic polysaccharide derivatives have been engineered from these natural precursors. Trimethyl chitosan (TMC) introduces quaternary ammonium groups that retain mucoadhesiveness while extending aqueous solubility across a broader pH range, favoring oral and nasal delivery. Thiolated chitosan, modified with sulfhydryl groups, forms disulfide bonds with mucus glycoproteins, extending mucosal residence time. Acetalated dextran (Ac-Dex) is acid-responsive, degrading rapidly within acidic endosomal compartments to facilitate intracellular drug release and

antigen presentation. Methacrylated hyaluronic acid (HAMA) enables photo- or chemically initiated hydrogel crosslinking for controlled site-specific release from injectable or implantable depots [49].

The conversion of natural polysaccharides into semi-synthetic derivatives allows fine-tuning of delivery kinetics and targeting precision, combining the inherent biocompatibility of the parent material with purpose-built functionality. Marine, animal, plant, and microbial sources each confer distinct structural and functional advantages, and through strategic modification these materials collectively provide a robust platform for engineering delivery systems that protect sensitive therapeutics, promote mucosal adherence, and enable controlled release contributing meaningfully to infectious disease control (Fig. 3) [50].

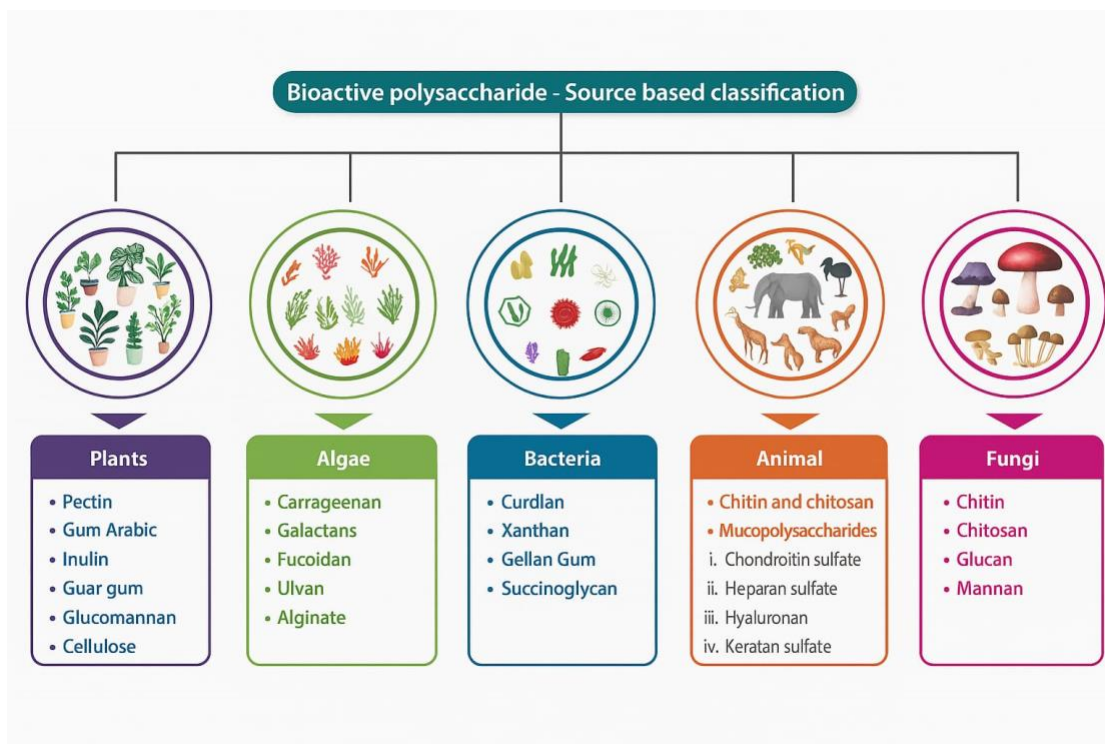


Fig. 3. Principal sources of polysaccharides used in drug delivery.

3.2 Selection Criteria for Drug Delivery Applications

Classifying polysaccharides by origin and chemistry provides a practical framework for selecting appropriate candidates for drug and vaccine delivery. Whereas Fig. 3 summarizes this classification by biological source (plant, algal, bacterial, animal, fungal) for quick visual reference, Table 3 below complements it with the structural features, typical chemical modifications, and representative delivery applications of

each polysaccharide type. At the most fundamental level, polysaccharides fall into two families: natural polymers sourced from animals, plants, microbes, and marine organisms, and semi-synthetic derivatives chemically modified to enhance solubility, responsiveness, mucoadhesion, or targeting. Among the natural materials, chitosan extracted from crustacean or fungal chitin contains cationic amine groups that confer mucoadhesive and mucosal-penetrating properties, making it well suited to nasal and oral

vaccine delivery; its dual role as carrier and mild adjuvant is well documented [51]. Alginate, an anionic copolymer of mannuronic and guluronic acids derived from brown algae, forms ionotropic gels with calcium ions, creating gentle matrices ideal for encapsulating proteins and live-attenuated vaccines [52]. Dextran, a microbial exopolysaccharide, is highly water-soluble and chemically versatile; derivatives such as carboxymethyl-dextran are widely used in hydrogels, conjugates, and nanoparticles [53]. Starch, obtained from corn, potato, or rice, offers cost-effective, enzymatically degradable matrices for oral and gastro-targeted systems and is readily converted into carboxymethyl or crosslinked forms for modified-release applications [54]. Hyaluronic acid, a glycosaminoglycan native to the extracellular matrix, interacts with CD44 receptors on immune and epithelial cells, forming viscous, biocompatible depots and hydrogels for targeted delivery [55].

Beyond these five core materials, numerous chemically tailored polysaccharides address specific formulation challenges [56], including N-trimethyl chitosan and thiolated chitosan for enhanced solubility and covalent mucoadhesion; oxidized alginate for Schiff-base crosslinking; acid-labile acetalated dextran (Ac-Dex) for pH-triggered intracellular release; carboxymethyl starch; methacrylated hyaluronic acid; carboxymethyl cellulose; and PEGylated or grafted polysaccharides for stealth behavior and active targeting. Ac-Dex, for example, enables acid-sensitive release within

endosomal compartments and has been explored for vaccine and anti-infective payloads, its facile fabrication into nano- and microparticles making it attractive for thermostable, single-dose formulations [56].

This classification is functionally instructive: native polysaccharides confer biocompatibility and biodegradability, while chemical modification introduces specialized functionality tailored to specific infectious disease applications mucoadhesion for intranasal vaccines (chitosan, TMC, thiolated chitosan), gentle encapsulation and oral protection for enteric vaccines (alginate, carboxymethyl starch), receptor-mediated targeting of antigen-presenting cells (HA, HAMA), and pH- or redox-responsiveness for intracellular antigen release (Ac-Dex, oxidized dextran). Recent studies further indicate that combining multiple polysaccharide types of chitosan–alginate composites or starch–alginate blends, for example can yield synergistic gains in mechanical stability, controlled release, and immunogenicity that are not achievable with a single polymer alone [57].

In summary, the classification of polysaccharides into natural and semi-synthetic families, exemplified by the materials discussed above, provides a rational basis for designing delivery systems that balance safety, manufacturability, and the specialized functional requirements of modern vaccines and anti-infective therapeutics.

Table 3. Classification of polysaccharides by structural features and applications.

S. No	Polysaccharide (Type)	Key Structural Features	Typical Modifications	Representative Applications	Ref.
1	Chitosan (natural)	Linear β -(1 $\rightarrow$ 4)-D-glucosamine; cationic	Quaternization, thiolation, PEGylation	Mucoadhesive nanoparticles, oral/gut delivery, mucosal vaccines	[58,59]
2	N-trimethyl chitosan (TMC)	Quaternary ammonium groups; soluble at neutral pH	N-methylation	Paracellular transport, soluble adjuvant coatings	[59,60]
3	Thiolated chitosan (TCS)	-SH groups on chitosan backbone	Cysteine/mercaptoalkyl grafting	Covalent mucoadhesion, prolonged mucosal residence	[58,61]
4	Alginate (natural)	β -D-mannuronic & α -L-guluronic acids; anionic	Oxidation, grafting, Ca ²⁺ crosslinking	Oral/injectable hydrogels, protein/vaccine encapsulation	[62,63]
5	Oxidized alginate	Aldehyde-functionalized alginate	Periodate oxidation	Injectable depots, antigen conjugation, tunable degradation	[61]
6	Dextran (natural)	Branched α -(1 $\rightarrow$ 6) glucose; hydroxyl-rich	Carboxymethylation, oxidation, acetalation	Drug conjugates, macrophage-targeted nanoparticles	[34,63]

7	Acetalated dextran (Ac-Dex)	Acid-labile acetal linkages	Cyclic/acyclic acetalation	pH-sensitive antigen release, thermostable vaccines	[54,64]
8	Starch (natural)	Amylose/amylopectin mix; enzyme-degradable	Carboxymethylation, grafting	Oral tablets, colon-targeted carriers	[65,66]
9	Modified starch	Etherified starch backbone	Crosslinking, carboxymethylation	GI-stable micro/nanoparticles for antigen delivery	[67]
10	Hyaluronic acid (HA)	Glucuronic acid-N-acetylglucosamine; CD44 ligand	Methacrylation, thiolation, PEGylation	CD44-targeted delivery, injectable hydrogels	[68,69]
11	Methacrylated HA (HAMA)	Photocrosslinkable methacrylate groups	Methacrylation	Implantable scaffolds, controlled antigen release	[70]
12	Pullulan (natural)	α -(1→6) maltotriose units; water-soluble	Oxidation, esterification, grafting	Antigen-stabilizing films, mucoadhesive patches	[71]
13	Pectin (natural)	Galacturonic acid-rich; Ca ²⁺ gelation	Amidation, crosslinking	Colon-targeted oral delivery, topical hydrogels	[72]

3.3 Key Functional Attributes: Biodegradability, Biocompatibility, and Mucoadhesion

Among the attributes that render polysaccharides suitable for drug delivery, biodegradability is foremost. Upon administration, these biopolymers undergo enzymatic hydrolysis or natural decomposition, yielding non-toxic byproducts monosaccharides or oligosaccharides that are metabolized or excreted without bioaccumulation. This intrinsic degradability allows precise modulation of release kinetics, supporting rapid release for antimicrobial agents or sustained antigen presentation for vaccines. Formulation parameters such as molecular weight, degree of crosslinking, and chemical modification can be adjusted to align degradation profiles with therapeutic objectives [73]. In vaccine delivery specifically, gradual degradation supports depot formation, prolonging antigen release, enhancing immunogenicity, and reducing dosing frequency; biodegradability therefore ensures physiological compatibility while also augmenting therapeutic efficacy through synchronized release behavior.

Equally important is the intrinsic biocompatibility of polysaccharides, which underpins their safe administration. Owing to their structural resemblance to endogenous carbohydrates, polysaccharides typically show low toxicity and minimal immunogenicity, making them suitable carriers for sensitive biomolecules such as proteins, peptides, and nucleic acids. Select polysaccharides additionally possess immunomodulatory properties that can be harnessed to enhance vaccine efficacy by activating antigen-presenting cells without inducing systemic inflammation. Molecular engineering approaches for instance, tuning the degree of

deacetylation of chitosan, or selecting alginate fractions of defined molecular weight allow biocompatibility to be balanced against clinical efficacy [74]. Relative to synthetic polymers, which may carry long-term toxicity risk, polysaccharides generally offer a more favorable safety profile for sustained therapeutic use.

Mucoadhesion represents a third pivotal property, particularly relevant to mucosal vaccine delivery. Because many pathogens initiate infection at mucosal surfaces respiratory, gastrointestinal, or urogenital targeting these sites is strategically advantageous. Mucoadhesive polysaccharides interact with the mucus layer through hydrogen bonding, electrostatic interaction, and hydrophobic forces, prolonging residence time and enhancing drug absorption. This retention protects labile molecules from premature clearance and facilitates antigen contact with mucosal immune cells, which are central to initiating both local and systemic immune responses. Chitosan, alginate, carrageenan, and cellulose derivatives are well-characterized examples of mucoadhesive polysaccharides [75]. Chemical modifications such as thiolation or cationization further enhance mucoadhesive strength and can promote paracellular transport by transiently opening tight junctions a mechanism relevant to inducing secretory IgA responses in oral and intranasal vaccine platforms.

The synergistic combination of biodegradability, biocompatibility, and mucoadhesion positions polysaccharide-based delivery systems as effective tools for combating infectious disease [76]: biodegradability ensures safe clearance and controlled release, biocompatibility supports therapeutic integrity with minimal adverse effects, and mucoadhesion enables targeted interaction at pathogen

entry sites. Advanced delivery formats nanoparticles, hydrogels, films, and microneedle arrays are increasingly engineered to optimize these attributes, and in response to growing demand for needle-free, patient-centric solutions,

polysaccharides provide a compelling foundation for next-generation drug and vaccine delivery technologies [77].

Table 4. Comparative properties of polysaccharides in drug and vaccine delivery.

Property	Chitosan	Alginate (SA)	Hyaluronic Acid (HA)	Dextran / Ace-DEX	Pullulan	CMC	Pectin	Ref.
Biodegradability	Enzymatic (chitinases, lysozyme); rate depends on MW	Ion exchange & enzymatic gel erosion	Hyaluronidases; MW-dependent	Dextran: enzymatic; Ace-DEX: acid-labile	Moderate enzymatic breakdown	Readily biodegradable	Pectinases; esterification-dependent	[78]
Biocompatibility / toxicity	Generally safe; cationic nature modifiable	Excellent; widely used	Endogenous; clinically approved	Favorable safety profile	Low immunogenicity	Excipient-grade; crosslinker-dependent	Widely used; low toxicity	[52]
Mucoadhesion / surface interactions	Strong (electrostatic with mucins)	Moderate (gel swelling)	Limited; receptor-binding (CD44)	Low; modifiable	Moderate; film-forming	Good; hydrogen bonding	Moderate; colon-targeting	[79]
Solubility / processability	Soluble in dilute acids; modifiable	Water-soluble; Ca ²⁺ gelation	Highly hydrophilic; forms hydrogels	Dextran: aqueous; Ace-DEX: organic solvents	Excellent film-forming	Water-soluble; hydrogel-forming	Water-soluble; gelation via Ca ²⁺	[80]
Immunomodulatory / adjuvant effects	Intrinsic antimicrobial & adjuvant	Mild bioactivity; wound applications	Receptor-mediated immune modulation	Enhances antigen presentation	Generally inert; modifiable	Inert; additive-dependent	Source-dependent immunomodulation	-
Stability (chemical & physical)	Depends on deacetylation; crosslinking improves	Stable gels; ion-sensitive	Hygroscopic; crosslinking improves	Tunable (pH-sensitive)	Good film stability	Stable when crosslinked; composites improve	Esterification-dependent	[81]
Controlled / stimuli-responsive release	Excellent; pH, thiol, enzyme-responsive	Very good; pH/ion-responsive	Enzyme/receptor-triggered; microneedles	Acid-sensitive intracellular release	Modifiable for redox/pH/enzyme	Swelling/crosslinking control	Enzyme/pH-responsive; colon targeting	[82]

3.4 Chemical Functionalization for Enhanced Delivery Performance

Polysaccharides possess a rich array of functional groups hydroxyl ($-\text{OH}$), amino ($-\text{NH}_2$), carboxyl ($-\text{COOH}$), aldehyde ($-\text{CHO}$), and vicinal diols that render them highly amenable to chemical modification, thereby enhancing their utility in drug and vaccine delivery (Fig. 4, Table 5) [83]. These modifications influence key physicochemical and biological properties, including solubility, biodegradability, structural stability, immune recognition, and site-specific delivery, and facilitate drug conjugation, targeted-ligand attachment, and responsiveness to physiological stimuli such as pH or enzymatic activity. Collectively, they enable the fabrication of diverse architectures nanoparticles, hydrogels, micelles, films, scaffolds, and mucoadhesive depots that support targeted delivery, protection of labile biomolecules, controlled release, and enhanced cellular uptake [8,9].

One of the most widely applied modifications is quaternization of amino groups, particularly in chitosan. This introduces permanent positive charge, improving hydrophilicity, mucoadhesion, and electrostatic interaction with negatively charged biomolecules such as DNA or RNA-based vaccine constructs [84]. Carboxymethylation or carboxylation, conversely, introduces negatively charged groups that impart amphiphilic character and enable ionic interaction with cationic drugs or metal ions, while also

providing anchoring sites for antigen or adjuvant conjugation via carbodiimide-mediated coupling.

Sulfation and phosphorylation introduce substantial negative charge in a heparin-like fashion, facilitating protein binding, immune modulation, and antiviral activity, and thereby expanding the role of polysaccharides as vaccine adjuvants [85]. Thiolation, through incorporation of sulfhydryl groups, enables disulfide bond formation for redox-sensitive intracellular drug release and enhances mucoadhesion via thiol–disulfide exchange with mucosal glycoproteins.

Periodate oxidation of vicinal diols generates aldehyde groups capable of forming Schiff bases with the amino groups of proteins or peptides, a reaction widely exploited in the development of glycoconjugate vaccines to achieve stable, targeted antigen presentation [86]. The incorporation of hydrophobic or polymerizable moieties acyl, alkyl, or methacrylate groups introduces amphiphilicity and crosslinking potential, promoting self-assembly into nanoparticles, hydrogels, or micelles for controlled drug and antigen release [87]. Collectively, these functional modifications enable the rational design of polysaccharide-based platforms with tailored delivery characteristics, from enhanced mucoadhesion and targeted release to immune potentiation, positioning polysaccharides as promising candidates for next-generation vaccines and anti-infective therapeutics [88].

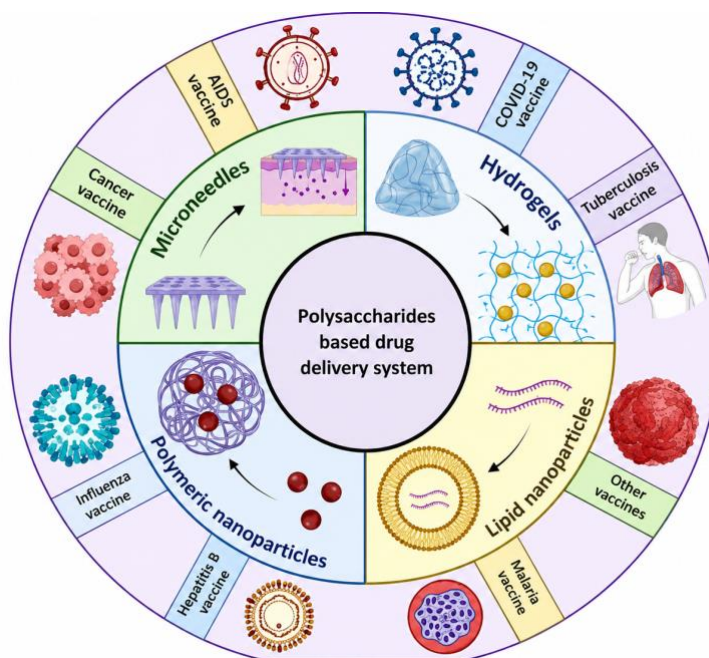


Fig. 4. Key functional groups enabling polysaccharide modification for advanced drug delivery.

Table 5. Functional groups in polysaccharides and their chemical modifications for drug delivery.

S.No	Functional Group	Example Polysaccharides	Common Chemical Modifications	Applications in Drug Delivery	Ref.
1	Hydroxyl (-OH)	Cellulose, starch, dextran, chitosan	Etherification, esterification, oxidation, PEGylation, acetylation	Improves solubility, stability, and controlled drug release; enhances mucoadhesion and biocompatibility	[89]
2	Amino (-NH ₂)	Chitosan, galactosamine-based polysaccharides	Acylation, quaternization, amidation, grafting with targeting ligands	Provides cationic character for gene/drug delivery, improves cell binding, enhances mucoadhesion, enables pH-responsive release	[90]
3	Carboxyl (-COOH)	Alginate, hyaluronic acid, pectin	Amidation, esterification, carbodiimide coupling	Enhances crosslinking, conjugation with bioactive molecules, improves drug encapsulation and targeting	[91]
4	Sulfate (-OSO ₃ -)	Heparin, carrageenan, dextran sulfate	Sulfation, desulfation, functional conjugation with proteins/ligands	Improves anticoagulant, antiviral, and anti-inflammatory properties; useful in nanoparticle stabilization	[92,93]
5	Carbonyl (C=O; aldehyde/ketone)	Oxidized cellulose, periodate-oxidized polysaccharides	Schiff-base formation, reductive amination, crosslinking with amines	Enables covalent drug conjugation, hydrogel formation, and stimuli-responsive systems	[94]
6	Acetal/hemiacetal (-O-C-O-)	Starch, pullulan, dextran	Crosslinking, hydrolysis-sensitive linkages	Used in pH-sensitive and enzyme-responsive delivery systems	[95]
7	Thiol (-SH) (introduced synthetically)	Thiolated chitosan, thiolated hyaluronic acid	Thiolation, disulfide crosslinking	Enhances mucoadhesion, provides redox-responsive release in tumor and intracellular environments	[96]

3.5 Tunable Properties of Polysaccharides for Vaccine and Drug Delivery

Polysaccharide-based platforms offer a versatile foundation for drug and vaccine delivery in infectious disease management owing to their tunable physicochemical properties and favorable biological interactions. At the molecular level, reactive hydroxyl, carboxyl, and amino groups facilitate straightforward chemical derivatization through crosslinking or conjugation with ligands, adjuvants, or antigens [97]. This modular chemistry allows precise control over key formulation parameters hydrophilicity–hydrophobicity balance, degradation rate, charge density, and network mesh size supporting the design of systems with sustained, stimuli-responsive, or site-specific release. Alginate and thiolated alginate, for example, form ionically or disulfide-crosslinked hydrogels with tunable gelation and

swelling behavior suited to oral or mucosal antigen protection, while hyaluronic acid derivatives enable receptor-targeted delivery via CD44 [98].

Polysaccharides are adaptable across multiple carrier formats nanoparticles, microparticles, hydrogels, films, microneedles, and coating layers allowing alignment with diverse administration routes (oral, nasal, intradermal, parenteral). Their intrinsic hydrophilicity supports efficient encapsulation and dispersion of hydrophilic payloads such as proteins, peptides, and nucleic acids, and particulate systems can be engineered with narrow size distributions to enhance uptake by antigen-presenting cells and lymphoid tissue. Many polysaccharide carriers also protect labile antigens from enzymatic or acidic degradation during gastrointestinal transit, improving mucosal bioavailability [99].

From a materials-engineering perspective, polysaccharides can be surface-functionalized or applied as layer-by-layer coatings to refine stability, release kinetics, and targeting specificity. Surface ligands such as mannose, peptides, antibodies, or charge-tuned moieties can direct trafficking toward dendritic cells, M cells, or epithelial transcytosis pathways, enhancing immune presentation while minimizing off-target exposure. Hybrid systems that combine polysaccharides with synthetic polymers or lipids can overcome mechanical or moisture-sensitivity limitations without compromising biodegradability or biocompatibility [99].

Biologically, polysaccharides are well tolerated in vivo, produce non-toxic metabolites, and support repeated-dose regimens. Some, including chitosan and select plant-derived polysaccharides, exhibit intrinsic mucoadhesive and immunomodulatory activity: mucoadhesion prolongs antigen residence at mucosal inductive sites, while receptor-mediated interaction with pattern-recognition receptors (e.g., Toll-like receptors and lectins) can amplify immune responses without requiring potent exogenous adjuvants. This is particularly relevant to needle-free oral or nasal vaccine strategies, which aim to induce both mucosal IgA and systemic immunity against pathogens entering via mucosal surfaces [100].

It should be noted that the magnitude and even the direction of chitosan's intrinsic adjuvant effect are not uniformly agreed upon in the literature: reported potency varies with molecular weight, degree of deacetylation, and formulation route, and some studies report negligible or inconsistent adjuvanticity relative to established adjuvants under comparable conditions [141], with residual endotoxin or process impurities identified as a further confound in several of these mechanistic studies [137]. This variability, rather than a single settled mechanism, is the more accurate current picture and should temper claims of intrinsic immunomodulatory activity as a uniformly reliable design feature.

Beyond their biological and engineering merits, polysaccharide platforms offer translational advantages: derived from abundant renewable sources, they are cost-effective, compatible with mild processing conditions, and in some formulations reduce cold-chain dependence by stabilizing antigens in dry or matrix-bound form. The convergence of physicochemical tunability and biological compatibility positions polysaccharide-based systems as promising candidates for next-generation drug and vaccine delivery technologies for infectious disease [4].

3.6 Comparative Critical Analysis of Polysaccharide Carriers

Table 4 (Section 3.3) already compares the principal polysaccharide carrier's property-by-property; rather than duplicate it, this section synthesizes that evidence into an explicit trade-off assessment. Chitosan and hyaluronic acid offer the strongest active-targeting and mucoadhesive properties (Table 4) but carry the greatest sourcing- and purity-related immunogenicity-control burden, since intrinsic adjuvant activity is difficult to standardize across batches [58,141]. Cellulose derivatives, pullulan, and pectin sit at the opposite end: minimal intrinsic immunogenicity and mature, standardized manufacturing (a long history as pharmaceutical excipients), but comparatively little intrinsic targeting or adjuvant function without additional functionalization [39,40,41]. Alginate and dextran occupy an intermediate position, offering high encapsulation efficiency for hydrophilic and protein payloads with moderate manufacturing complexity, though native dextran can be immunogenic in rare cases and alginate's gelation behavior is sensitive to batch-to-batch viscosity [57,62,63,79]. This trade-off pattern, rather than any single universally superior polysaccharide, is what should guide carrier selection for a given indication, administration route, and manufacturing context, and it is why Table 4 is presented as a property comparison rather than a ranked list.

4. POLYSACCHARIDE-BASED DRUG DELIVERY SYSTEMS FOR ANTIMICROBIAL THERAPEUTICS

Polysaccharide-based drug delivery systems (DDS) present a versatile and clinically relevant platform for antimicrobial therapy, combining the safety of natural polymers with tunable chemistries that support encapsulation, conjugation, and nanoscale formulation, thereby addressing key limitations of conventional antimicrobials such as poor solubility, rapid degradation, and systemic toxicity. Mechanistically, polysaccharide DDS operate through three complementary strategies: encapsulation, chemical conjugation, and nanoparticle formation (Table 6). Encapsulation physically entraps antimicrobial agents antibiotics, peptides, or antivirals within hydrophilic matrices (e.g., alginate gels, dextran scaffolds) or particulate shells (e.g., chitosan coatings), protecting labile drugs and enabling controlled release at the infection site. Conjugation entails covalent attachment of drugs or prodrugs to the polysaccharide backbone, improving solubility, extending circulation half-life, and allowing stimuli-responsive cleavage (pH, redox, enzymatic) for site-specific activation. Nanoparticle formation exploits self-

assembly, ionic crosslinking, or polyelectrolyte complexation to produce carriers optimized for mucosal uptake, biofilm penetration, or intracellular delivery [101]. Together, these mechanisms enable two core therapeutic capabilities targeted delivery and sustained release. Targeting may be passive, governed by particle size and charge, or active, involving surface ligands (antibodies, peptides, sugars) that bind microbial receptors; chitosan's positive charge, for example, facilitates electrostatic interaction with bacterial membranes and mucosal surfaces, enhancing retention and localized drug release (Fig. 5). Sustained release is achieved by tuning crosslink density, degree of substitution, or the incorporation of cleavable linkers, maintaining therapeutic drug levels while minimizing systemic exposure and the selective pressure that drives resistance [102,103].

Translational examples illustrate the clinical relevance of these platforms. Chitosan nanoparticles, prepared via ionic gelation or self-assembly [104], have been used to encapsulate aminoglycosides, tetracyclines, β -lactams, and combination regimens; their intrinsic antimicrobial activity, mucoadhesion, and membrane-disruptive properties enhance antibiotic uptake and stability, and in vitro and in vivo studies report reduced minimum inhibitory concentrations (MICs), lower bacterial burden, and accelerated wound healing against resistant strains. Alginate-based hydrogels, formed via divalent-cation crosslinking, create conformable, exudate-absorbing matrices well suited to topical dressings; these can entrap antibiotics, antimicrobial peptides, metal ions (silver, zinc), or nanoparticles for sustained local release and biofilm inhibition, with tunable porosity and degradation aligning with the therapeutic timelines of acute and chronic wound management. Dextran conjugates offer a molecular strategy for antiviral delivery: covalent linkage improves solubility, reduces renal clearance, and enables multivalent interaction with viral envelopes or host receptors, and dextran sulfate derivatives in particular have shown promise in blocking viral attachment and entry or acting as long-circulating prodrugs, with pharmacokinetic and cell-based studies confirming enhanced potency and retention for select antiviral agents [105].

Beyond these individual examples, polysaccharide DDS address broader challenges in antimicrobial therapy. They increase local drug concentration at infection sites, reduce subtherapeutic systemic exposure, and support combination therapy within a single carrier. By targeting biofilms or intracellular reservoirs, these systems bypass barriers that otherwise shield pathogens from conventional drugs; localized, sustained release minimizes systemic toxicity, while entrapment or conjugation improves the bioavailability of poorly soluble agents, in some cases rescuing older drugs with otherwise unfavorable pharmacokinetics. Stimuli-responsive designs that exploit infection-associated cues (acidic pH, bacterial enzymes) enable “smart” release with improved selectivity. Illustrative case studies underscore these advantages: chitosan nanoparticles loaded with antibiotics have demonstrated reduced MICs and bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant Gram-negative strains, while peptide-loaded oxidized-dextran hydrogels have achieved greater than 95% wound closure together with significant biofilm reduction in preclinical models [106].

Despite these promising outcomes, translational challenges persist. Scalable manufacturing, batch-to-batch reproducibility, and long-term safety particularly for chemically modified polysaccharides must be more fully addressed, and regulatory complexity increases further for combination products such as device–drug hybrids, which require harmonized evaluation frameworks. Nonetheless, the clinical trajectory of polysaccharide formulations is accelerating, driven by global demand for solutions to antimicrobial resistance and supported by the inherent biocompatibility of these polymers. Through encapsulation, conjugation, and nanoparticle engineering, polysaccharide DDS offer a modular toolkit for delivering antibiotics, antivirals, and antifungals with enhanced precision, enabling localized deposition, sustained and stimuli-responsive release, improved bioavailability, and minimized off-target exposure. As formulation science matures and regulatory pathways for polymeric carriers become better defined, polysaccharide-based systems are well positioned to serve as next-generation therapeutics, particularly where conventional agents falter against resistant pathogens [96].

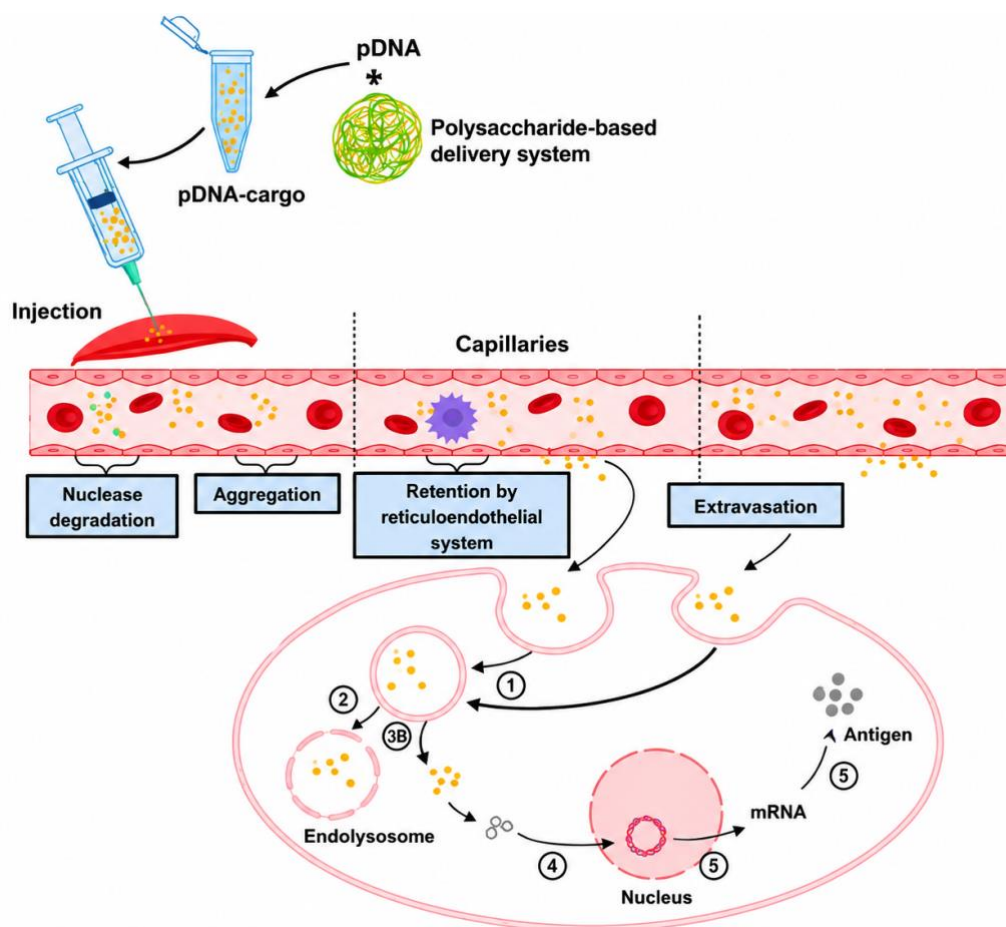


Fig. 5. Polysaccharide-based delivery systems enabling targeted, sustained antimicrobial therapy.

Table 6. Case studies of polysaccharide-based drug delivery systems for antimicrobial agents.

S.No	Polysaccharide	Antimicrobial Agent	DDS Formulation	Findings	Ref.
1	Chitosan	Vancomycin	Chitosan nanoparticle	Enhanced antibacterial activity against <i>S. aureus</i> ; improved drug stability with sustained release	[107]
2	Alginate	Ciprofloxacin	Alginate-chitosan nanocomplex	Improved oral bioavailability and controlled release; effective against multidrug-resistant bacteria	[108]
3	Hyaluronic acid	Silver nanoparticles	HA-coated AgNPs	Prolonged antibacterial effect with reduced cytotoxicity to mammalian cells	[109]
4	Dextran	Amphotericin B	Dextran-based micelles	Improved solubility and reduced nephrotoxicity while maintaining antifungal activity	[110]

5	Pullulan	Doxycycline	Pullulan nanofibers	Localized and sustained release for wound-infection treatment	[111]
6	Chitosan-hyaluronic acid	Levofloxacin	Polyelectrolyte complex nanoparticles	Increased retention time and targeted delivery for respiratory infections	[112]
7	Alginate	Curcumin	Alginate nanoparticles	Improved solubility and synergistic antimicrobial activity with antibiotics	[113]
8	Starch	Gentamicin	Starch-based hydrogels	Effective localized delivery with reduced systemic toxicity	[114]

5. POLYSACCHARIDE-BASED VACCINE DELIVERY SYSTEMS

Polysaccharides are emerging as versatile biomaterials for the design of modern vaccine delivery systems targeting infectious disease. Their structural diversity, biocompatibility, biodegradability, and tunable physicochemical properties make them well suited as carriers that stabilize fragile antigens while enhancing immune responses through both passive and active mechanisms. Polysaccharide-based platforms are compatible with multiple delivery formats nanoparticles, microparticles, hydrogels, and scaffolds and support oral,

nasal, and injectable administration [115,116]. Compared with conventional vaccine constructs, which often suffer from poor antigen stability, rapid clearance, and cold-chain dependence, polysaccharide systems offer improved antigen preservation, mucosal immunity, and dose sparing (Fig. 6). The following subsections discuss the roles of polysaccharides in antigen stabilization, intrinsic adjuvant activity, delivery-format innovation, and the specific contributions of chitosan, dextran, and alginate, together with their comparative advantages over classical vaccine platforms [100].

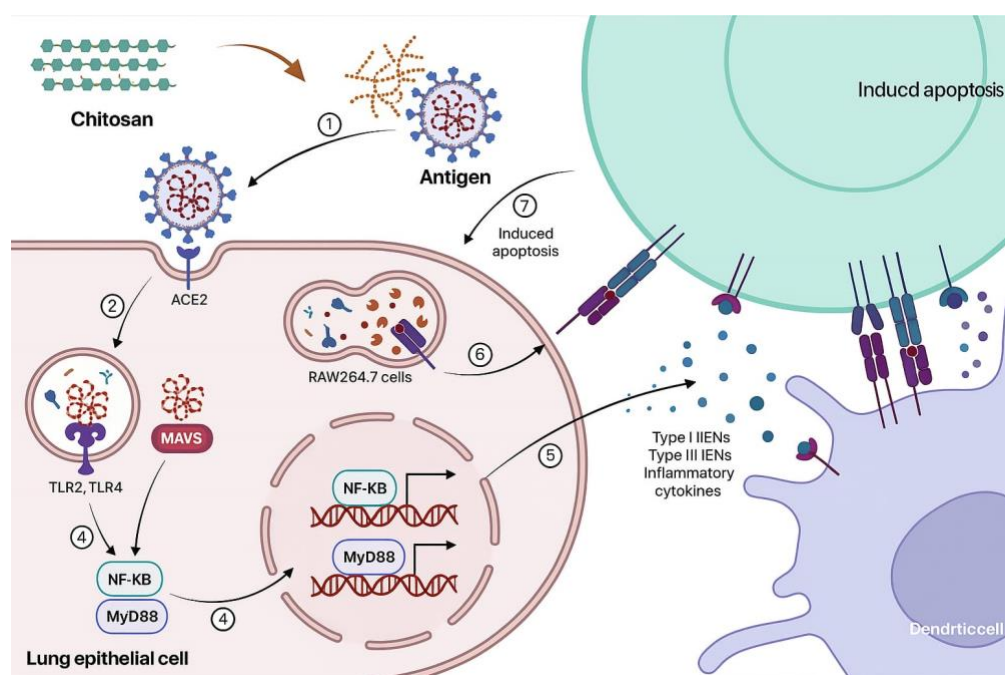


Fig. 6. Polysaccharide-based vaccine delivery systems enhance antigen stability and immune response.

5.1 Mechanisms of Antigen Stabilization and Protective Shielding

A major challenge in vaccine formulation is maintaining antigen integrity during storage, distribution, and

administration: the proteins, peptides, and nucleic acids used as antigens are prone to denaturation, enzymatic degradation, and aggregation, all of which reduce immunogenicity. Polysaccharide-based systems mitigate these risks by providing a protective matrix encapsulation within

nanoparticles, microparticles, or hydrogels shields antigens from gastrointestinal conditions, proteolytic enzymes, and oxidative stress (Fig. 7). Alginate, for example, exerts a strong protective effect on protein antigens during gastrointestinal transit, preserving antigenicity until mucosal delivery and immune induction occur [9,98], while dextran derivatives stabilize conjugated peptides against hydrolytic degradation, extending their functional lifespan [60].

Beyond in vivo protection, polysaccharides also enhance antigen stability during manufacturing and storage. Their capacity to form viscous networks or glassy matrices helps maintain proteins in near-native conformations, reducing reliance on cold-chain logistics a feature of particular value for improving vaccine accessibility in resource-limited settings. Unlike conventional adjuvants, polysaccharides can simultaneously serve as stabilizers and delivery vehicles, simplifying overall formulation design.

5.2 Adjuvant Potential for Enhanced Immune Activation

Polysaccharides function not only as carriers but also as immunomodulators. Chitosan and β -glucans, for example, engage pattern-recognition receptors such as Toll-like receptors, C-type lectins, and scavenger receptors, triggering

innate immune signaling; activation of dendritic cells and macrophages leads to upregulation of co-stimulatory molecules and cytokines, bridging innate and adaptive immunity [117,118]. This dual functionality supports the development of formulations with built-in adjuvant effects (Fig. 7).

Chitosan has been extensively studied for its ability to elicit mucosal immune responses. Its cationic character facilitates interaction with negatively charged epithelial membranes, transiently opening tight junctions and promoting antigen translocation to mucosal antigen-presenting cells, a mechanism that supports induction of both local IgA and systemic IgG responses. Polysaccharides can additionally be functionalized with targeting ligands such as mannose to direct antigens toward dendritic cells via mannose receptors, further enhancing antigen presentation [100].

By serving simultaneously as delivery vehicles and immunostimulants, polysaccharides reduce the need for additional adjuvants and can minimize side effects commonly associated with conventional agents such as alum. This multifunctionality makes them attractive candidates for next-generation vaccine platforms, particularly those designed for mucosal delivery and broad global accessibility.

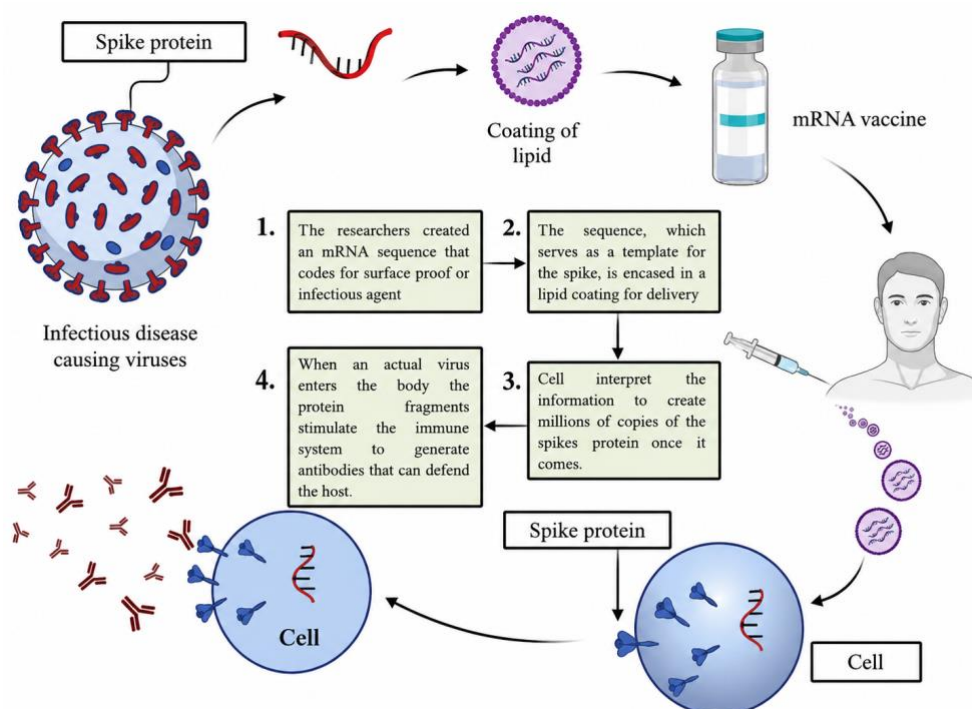


Fig. 7. Adjuvant potential of polysaccharides for improved immune activation in vaccines.

5.3 Innovative Platforms: From Nanoparticles and Hydrogels to Advanced Vaccine Systems

Polysaccharides underpin a broad spectrum of delivery platforms tailored to diverse immunological and clinical requirements. Nanoparticles and microparticles are the most extensively studied of these formats: their small size facilitates efficient uptake by dendritic cells and macrophages, while surface charge and functionalization can be tuned to influence biodistribution and immunogenicity. Chitosan nanoparticles, for example, have been used for nasal delivery of influenza antigens, eliciting robust mucosal and systemic immune responses [97], while dextran-based nanoparticles have been explored for co-delivery of multiple antigens with immunostimulatory molecules, enhancing the efficacy of subunit vaccines.

Hydrogels and scaffolds represent another promising delivery class. Polysaccharide hydrogels derived from alginate, hyaluronic acid, or dextran form three-dimensional networks that enable controlled, prolonged antigen release; such systems can approximate the immunological effect of prime-boost vaccination through single-dose administration, with temporally orchestrated delivery of antigen and adjuvant. By forming a depot at the injection site, hydrogels promote local immune cell recruitment and sustained antigen exposure, enhancing immunogenicity without repeated dosing [9].

Polysaccharide-based systems are also adaptable across administration routes. Oral vaccines, attractive for mass immunization, often face antigen degradation in the gastrointestinal tract; encapsulation in alginate or chitosan protects antigens during transit and facilitates targeted release in the intestine, improving uptake by Peyer's patches and stimulating mucosal immunity [98]. Chitosan's mucoadhesive and permeability-enhancing properties further support nasal vaccine formulations that promote strong IgA responses, while for injectable formats, polysaccharide scaffolds and conjugates act as depot systems that extend antigen release and induce systemic immune activation.

Collectively, these platforms illustrate the versatility of polysaccharide-based systems in addressing both mucosal and systemic infectious threats, and their compatibility with multiple formats and routes of administration positions them as key enablers of next-generation vaccine technology.

5.4 Chitosan, Dextran, and Alginate as Exemplary Vaccine Carriers

Among the polysaccharides evaluated as vaccine carriers, chitosan, dextran, and alginate have emerged as particularly well-studied models (Table 7), each offering distinct structural and functional advantages that support antigen stabilization, immune activation, and compatibility with diverse delivery routes.

Chitosan is among the most extensively studied polysaccharides for mucosal vaccine delivery. Its cationic character facilitates strong electrostatic interaction with negatively charged mucosal surfaces [119], enhancing residence time and antigen uptake; preclinical studies show that intranasal administration of influenza antigens encapsulated in chitosan nanoparticles induces robust systemic IgG and mucosal IgA responses, conferring protection against viral challenge [60]. Chitosan has also been evaluated for oral vaccine formulations, where it protects antigens from gastric degradation and promotes delivery to intestinal lymphoid tissue; derivatives such as N-trimethyl chitosan offer improved solubility and permeability, broadening applicability across mucosal platforms.

Dextran and its derivatives have been used in the development of conjugate vaccines. Linking bacterial polysaccharide antigens to a dextran backbone converts T-independent antigens into T-dependent forms, enhancing immunogenicity and enabling memory-response generation. Acetalated dextran, a pH-sensitive variant, degrades in acidic environments such as the phagosome, facilitating intracellular antigen release within antigen-presenting cells [118] positioning dextran not only as a passive scaffold but also as an active modulator of antigen presentation.

Alginate forms hydrogel networks upon contact with divalent cations, making it well suited to oral vaccine delivery: encapsulation within alginate beads or nanoparticles protects antigens from gastric acidity and enables targeted release in the intestine. Alginate-based oral vaccines have demonstrated the capacity to induce both mucosal and systemic immunity, with applications spanning aquaculture through to human enteric vaccines [9,98], and its biocompatibility and scalable gel-forming properties make it a leading candidate for mass-produced oral platforms.

Relative to conventional vaccine formulations typically simple mixtures of antigen and adjuvant polysaccharide-based systems offer several advantages: they stabilize antigens,

reduce cold-chain dependency, and extend shelf life, all of which are critical for deployment in low-resource settings. Their capacity to induce mucosal immunity, particularly secretory IgA responses, provides frontline defense against pathogens entering via the respiratory or gastrointestinal route, while controlled and sustained antigen release reduces the need for booster doses, improving coverage during pandemics or in underserved populations [97].

Nonetheless, clinical translation of polysaccharide-based vaccine platforms faces real challenges. Natural variability across polysaccharide batches and their inherent structural complexity can complicate regulatory approval, and scalable, reproducible manufacturing of nanoparticles and hydrogels must meet stringent quality-control standards. Moreover,

while preclinical data are promising, direct clinical comparisons with licensed adjuvants such as alum or MF59 remain limited, and continued clinical evaluation is required to establish comparative efficacy and safety.

In summary, polysaccharide-based vaccine delivery systems represent a unified platform integrating antigen protection, immune stimulation, and delivery versatility. Chitosan, dextran, and alginate exemplify the potential of these systems across mucosal, conjugate, and oral vaccine strategies, and with further validation and regulatory alignment, polysaccharide platforms may augment or in specific contexts surpass traditional vaccine technologies, particularly where stability, accessibility, and mucosal immunity are paramount.

Table 7. Polysaccharide-based delivery systems for vaccines against infectious diseases.

S. No	Polysaccharide Carrier	Vaccine Type	Administration Route	Reported Outcomes	Ref.
1	Chitosan NPs (e.g., mannose-conjugated)	Protein subunit (SARS-CoV-2 RBD)	Intranasal	Strong mucosal sIgA and T-cell responses; reduced viral load; enhanced APC uptake; dose-sparing potential	[120]
2	Alginate NPs/gels	Multi-epitope protein	Oral / injectable	GI protection of antigen; enhanced IgG and Th1/Th2 responses; improved antigen stability	[121]
3	HA hydrogels / cryogels	Protein subunit (e.g., OVA)	Subcutaneous depot	Sustained antigen release; higher antibody and T-cell responses; durable immunity; dose-sparing	[122]
4	Dextran / Ace-DEX microparticles	Subunit / conjugate vaccines	Injectable / mucosal	pH-sensitive release; enhanced antigen presentation; robust immune responses; improved thermostability	[53,123]

6. MARKETED POLYSACCHARIDE-BASED PLATFORMS IN DRUG AND VACCINE DELIVERY

Polysaccharides have already been translated successfully into commercial vaccines and therapeutic products, functioning as antigen carriers, adjuvants, and stabilizing matrices. Table 8 summarizes representative licensed products, spanning pneumococcal, Haemophilus influenzae

type b, meningococcal, and typhoid conjugate vaccines, as well as chitosan-adjuvanted veterinary formulations. These examples provide direct clinical and commercial validation that polysaccharide chemistry can be translated at scale into products meeting regulatory approval, and they establish an important precedent for the emerging nanoparticle- and hydrogel-based platforms discussed elsewhere in this review.

Table 8. Marketed polysaccharide-based platforms for infectious disease control.

S.No	Product / Technology	Polysaccharide Used	Application / Indication	Commercial Status / Route	Ref.
1	Pevnar 13 / Pevnar 20	Capsular polysaccharides (conjugated to CRM197 protein)	Pneumococcal disease prevention	Marketed, intramuscular	[124]
2	VAXNEUVANCE (PCV15)	Capsular polysaccharides conjugated to carrier proteins	Pneumococcal disease	Marketed, IM (Merck)	[125]
3	Liquid PedvaxHIB	Haemophilus influenzae type b PRP polysaccharide conjugate	Hib disease prevention	Marketed, IM (Merck)	[126]
4	Pentacel / VAXELIS	Hib PRP polysaccharide conjugated with other vaccines	Combination pediatric vaccines	Marketed, IM (Sanofi, MCM Vaccine)	[127]
5	Menactra / Menveo / Nimenrix	Capsular polysaccharides of Neisseria meningitidis conjugated to proteins	Meningococcal meningitis prevention	Marketed worldwide, IM	[128]
6	Typhim Vi	Purified Vi capsular polysaccharide of Salmonella Typhi	Typhoid fever prevention	Marketed, IM/subcutaneous (Sanofi)	[129]
7	CaniLeish	Chitosan-based adjuvant matrix with Leishmania antigens	Canine visceral leishmaniasis vaccine	Veterinary marketed (Europe)	[130]
8	LetiFend	Chitosan-stabilized recombinant protein formulation	Canine leishmaniasis	Veterinary marketed (Europe)	[131]

Beyond these licensed products, clinical evidence for polysaccharide-based delivery specifically is strongest for the conjugate vaccine platforms in Table 8, several of which report multi-year immunogenicity persistence and booster efficacy in randomized trials [127,128], and considerably weaker for the nanoparticle-, hydrogel-, and mucoadhesive-carrier systems discussed elsewhere in this review, most of which remain at the preclinical or early Phase I/II stage. Commercialization pathways for these newer platforms therefore differ substantially from those of the marketed conjugate vaccines: whereas conjugate-vaccine manufacturing benefits from decades of process standardization, nanoparticulate and hydrogel-based carriers must still establish reproducible large-scale synthesis, validated sterilization methods, and agreed critical-quality-attribute specifications before regulatory filings can proceed [103,139], a gap explored further in Section 7.

7. TRANSLATIONAL CHALLENGES AND STRATEGIC CONSIDERATIONS

Polysaccharide-based delivery systems hold considerable promise for combating infectious disease, yet several translational hurdles must be addressed before this potential can be fully realized. Formulation stability is among the foremost challenges: polysaccharides and their associated payloads proteins, peptides, or nucleic acids are often sensitive to manufacturing stresses such as pH fluctuation, shear force, dehydration, sterilization, and thermal exposure, conditions that can drive aggregation, structural degradation, or loss of biological activity. Even after formulation, residual moisture and excipient interactions may compromise matrix integrity, reduce shelf life and necessitate cold-chain logistics. Advances in excipient design and drying technology are addressing this issue, but thermostability remains formulation-specific and difficult to generalize across platforms and payloads [132,133].

A second persistent limitation is the lack of reproducibility and scalability. Unlike synthetic polymers, polysaccharides are inherently heterogeneous in molecular weight, branching,

and degree of acetylation or purity [116], and this variability affects how processing parameters pH, ionic strength, crosslinker concentration influence nanoparticle or hydrogel formation. As a result, formulations optimized at laboratory scale often fail to retain their physicochemical characteristics upon industrial scale-up, producing inconsistencies in particle size, drug loading, and release kinetics [102]. Achieving batch-to-batch reproducibility with consistent functionality remains a significant barrier to commercialization [102,103,116].

Regulatory complexity further impedes clinical translation. Existing frameworks for drugs and biologics are not fully equipped to evaluate polysaccharide-based carriers, particularly when configured as hybrid nanostructures or conjugated systems. Regulatory agencies require detailed characterization of raw materials, residual impurities, endotoxin levels, and critical quality attributes such as particle size and surface charge, together with validated assays for stability and potency [105]; however, international harmonization of analytical methods and acceptance criteria remains a work in progress. Natural variability in polysaccharide sourcing further complicates traceability and excipient standardization, potentially delaying approval timelines and increasing development costs.

Immunogenicity and unintended biological responses represent a further concern. Although polysaccharides are generally biocompatible and biodegradable, structural motifs or residual impurities can trigger adverse immune reactions, including complement activation, hypersensitivity, or immune suppression. While immunostimulatory activity is desirable in a vaccine context, uncontrolled responses pose risk in therapeutic applications requiring repeated dosing; the extent of chemical modification, residual protein or endotoxin contamination, and structural heterogeneity all influence immunological outcome, underscoring the need for rigorous immunotoxicological assessment during preclinical and clinical development [96,103,106].

Despite these challenges, polysaccharide-based delivery systems offer a compelling opportunity to advance vaccine and therapeutic delivery. Addressing the limitations outlined above will require integrated solutions: standardized sourcing of raw materials, implementation of process analytical technologies to monitor critical quality attributes, excipient optimization for enhanced stability, and early engagement with regulatory bodies. With such strategies in place (Table 9), the potential of polysaccharide platforms to help control communicable disease can be more fully realized.

Table 9. Challenges in formulating polysaccharide-based delivery systems.

S.No	Challenge	Impact on Formulation	Representative Example	Ref.
1	Raw-material variability	Affects viscosity, gelation, and drug loading	Alginate batches altered gel strength and release	[134]
2	Physicochemical instability	Hydrolysis/depolymerization affects shelf life	Chitosan NPs degraded during aqueous storage	[135]
3	Sterilization & endotoxin	Degradation or LPS contamination affects safety	LPS caused misleading immune activation	[136]
4	Gelation/crosslinking control	Sensitive to pH, ion concentration, mixing	Ca ²⁺ method altered alginate bead consistency	[134,135]
5	Mechanical weakness & moisture sensitivity	Limits solid formats like microneedles	Microneedles softened without polymer blending	[136]
6	Encapsulation & release of labile biomolecules	Protein/nucleic acid loss during processing	Antigen denaturation reduced immunogenicity	[137]
7	Analytical & QC limitations	Poor standardization hinders regulatory approval	In vitro-in vivo mismatch in release assays	[138]

8	Scalability issues	Lab methods fail to scale with consistency	Size/encapsulation altered during scale-up	[139]
9	Regulatory & clinical translation	GMP, stability, and impurity control complex	Raw-material specs delay clinical progress	[140]
10	Variable immunostimulation	Structural differences affect immune response	Chitosan deacetylation altered adjuvanticity	[141]

8. FUTURE PERSPECTIVES

Polysaccharide-based drug and vaccine delivery systems are positioned to play a central role in the next generation of therapeutic technologies for infectious disease management. Their intrinsic biocompatibility, biodegradability, and chemical versatility provide a strong foundation for advanced delivery platform design, and future development is expected to focus on the rational engineering of systems with precise control over physicochemical and biological properties to improve targeting, stability, and therapeutic efficacy [142].

A key direction is the development of stimuli-responsive, “smart” delivery systems. Chemical modifications incorporating dynamic linkages hydrazone, disulfide, and imine bonds enable carriers to respond to environmental triggers including pH, enzymatic activity, redox gradients, and temperature, allowing site-specific and controlled release that is particularly valuable for mucosal, oral, and localized delivery. Such approaches are expected to advance precision medicine by minimizing off-target effects while improving treatment outcomes [143,144].

A second promising avenue is the integration of polysaccharides into hybrid, multifunctional nanoplateforms. Combinations with lipids, proteins, and inorganic nanomaterials have demonstrated potential to overcome the limitations of single-component systems: lipid–polysaccharide hybrids, for example, can improve intracellular delivery efficiency, while polysaccharide-coated metallic nanoparticles offer additional antimicrobial or adjuvant activity [145]. Future work must prioritize optimizing these systems with respect to toxicity, scalability, and long-term stability to ensure clinical applicability.

Polysaccharide carriers are also expected to contribute significantly to the advancement of next-generation vaccines, including mRNA-, DNA-, and recombinant antigen-based platforms [146]. Functionalized nanoparticles and hydrogels can protect nucleic acids from degradation, enhance cellular uptake, and stabilize antigens under thermal stress, reducing

dependence on cold-chain logistics; their capacity to support mucosal delivery further enables induction of both systemic and localized immunity, which is critical for combating respiratory and gastrointestinal pathogens [147]. Continued exploration of ligand-mediated targeting in combination with lipid nanoparticles may yield highly effective, needle-free immunization strategies.

Translational and manufacturing challenges nonetheless remain a critical bottleneck. Future research should address batch-to-batch variability through standardized sourcing and characterization of polysaccharides, and improve reproducibility through advanced manufacturing techniques such as microfluidics, continuous processing, and spray-drying [148]. Early integration of regulatory considerations compliance with good manufacturing practice (GMP) and validated analytical methods will be essential to accelerate clinical translation.

Emerging integration with nanotechnology, immunoengineering, and data-driven approaches represents a further transformative direction. Surface-functionalized polysaccharide carriers can be engineered to target antigen-presenting cells with high specificity, while hydrogel-based systems can provide sustained antigen release and immune priming; coupling these platforms with high-throughput tools such as single-cell sequencing and computational modeling may enable rational design of delivery systems tailored to specific immunological outcomes [149].

Finally, polysaccharide-based systems are well aligned with the principles of personalized medicine. Their modular nature allows customization of delivery platforms for patient-specific antigens, including tumor neoantigens or individualized microbial targets, and future development may incorporate biomarker-guided dosing and integration with digital health technologies to optimize therapeutic response across diverse populations.

These directions should be read against realistic constraints rather than as a straightforward roadmap. Regulatory approval

for hybrid or stimuli-responsive polysaccharide nanocarriers will likely take longer than for the conjugate-vaccine platforms already on the market, because agencies currently lack harmonized critical-quality-attribute definitions for these newer architectures [103]. GMP-compliant, large-scale manufacture of nanoparticulate or hydrogel systems with batch-to-batch consistency has not yet been demonstrated at the volumes required for global vaccination campaigns, and the cost of achieving that consistency – through process analytical technology, raw-material qualification, and validated sterilization – may offset some of the raw-material cost advantage that polysaccharides otherwise offer over synthetic polymers [139]. Long-term toxicity and immunogenicity data, particularly for chemically modified or hybrid carriers intended for repeated dosing, remain limited beyond the timeframes captured in most preclinical studies cited in this review, and endotoxin or impurity carry-over from raw polysaccharide sourcing remains an under-reported confound in adjuvanticity studies specifically [137], so the optimistic translational timeline implied by current preclinical activity should be tempered accordingly.

In summary, the future of polysaccharide-based delivery systems lies at the convergence of advanced materials engineering, nanotechnology, and immunological insight. While challenges related to scalability, regulatory approval, and clinical validation persist, continued innovation and interdisciplinary collaboration are expected to enable the development of safe, effective, and accessible delivery platforms for global healthcare.

9. CONCLUSION

Polysaccharides are increasingly used as carriers for therapeutic drugs and vaccines targeting infectious disease owing to their safety, sustainability, and biocompatibility. These carriers protect against degradation, prolong circulation, and strengthen targeted immune responses. Antimicrobial resistance is a growing problem in modern medicine, and conventional drug delivery systems that yield subtherapeutic tissue concentrations contribute to the emergence of resistant strains; polysaccharide-based drug delivery systems enable targeted and controlled release, thereby reducing the likelihood of resistance development while increasing treatment efficacy. Certain polysaccharides chitosan and dextran derivatives among them possess intrinsic mucoadhesive properties well suited to targeting mucosal

surfaces at the point of pathogen entry, and polysaccharide scaffolds further support the fabrication of nanoparticles, microparticles, and hydrogels capable of engaging pattern-recognition receptors to mimic natural immune activation. Nonetheless, the transition of polysaccharide-based carriers from bench to market remains challenging, constrained by limited manufacturing scale-up and the still-early clinical stage of many candidate platforms. Continued innovation in sustainable, biodegradable polysaccharide chemistry can help accelerate the shift toward greener, more sustainable healthcare worldwide. In conclusion, polysaccharides represent a promising frontier for combating infectious disease, offering the potential for antimicrobial and vaccine platforms that are both less prone to driving resistance and highly effective clinically. As such, polysaccharide-based delivery systems form a promising bridge between biomaterials science and translational medicine, offering scalable, safe, and multifunctional platforms for next-generation therapeutics. Three points merit emphasis for readers weighing where the field genuinely stands. First, the major scientific advances are concrete rather than aspirational: marketed polysaccharide-conjugate vaccines (Table 8) and a growing set of chitosan- and alginate-based antimicrobial and wound-care products demonstrate that polysaccharide chemistry can be translated at commercial scale. Second, the remaining challenges are equally concrete and are concentrated at the interface of manufacturing and regulation – raw-material heterogeneity, batch-to-batch reproducibility, endotoxin and sterilization control, and the absence of harmonized critical-quality-attribute standards for hybrid nanostructured carriers (Section 7, Table 9) – rather than in the underlying biological rationale, which is comparatively well supported. Third, the highest-priority research needs going forward are standardized, source-traceable raw-material specifications; validated, scalable manufacturing platforms (e.g., microfluidic or continuous-flow production); and controlled clinical studies that directly compare polysaccharide-based carriers with existing standard-of-care delivery systems, since most of the evidence synthesized in this review remains preclinical. Addressing these three priorities, rather than further expanding the preclinical literature, is likely to determine how quickly polysaccharide-based platforms move from promising biomaterials to routine clinical tools for infectious disease control.

AUTHORS' CONTRIBUTIONS

All authors contributed substantially to the conception, literature review, writing, revision, and final approval of the manuscript. All authors have accepted responsibility for the content of the manuscript and consented to its submission. They have reviewed the final version and approved it for publication.

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Not applicable.

AVAILABILITY OF DATA AND MATERIALS

No new datasets were generated or analyzed during the current study. All data supporting the findings of this review are available within the published literature cited in the References section.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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