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Prophylactic vaccine delivery systems against epidemic infectious diseases

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ABSTRACT

Prophylactic vaccines have evolved from traditional whole-cell vaccines to safer subunit vaccines. However, subunit vaccines still face problems, such as poor immunogenicity and low efficiency, while traditional adjuvants are usually unable to meet specific response needs. Advanced delivery vectors are important to overcome these barriers; they have favorable safety and effectiveness, tunable properties, precise location, and immunomodulatory capabilities. Nevertheless, there has been no systematic summary of the delivery systems to cover a wide range of infectious pathogens. We herein summarized and compared the delivery systems for major or epidemic infectious diseases caused by bacteria, viruses, fungi, and parasites. We also included the newly licensed vaccines (e.g., COVID-19 vaccines) and those close to licensure. Furthermore, we highlighted advanced delivery systems with high efficiency, cross-protection, or long-term protection against epidemic pathogens, and we put forward prospects and thoughts on the development of future prophylactic vaccines.

Contents

Abbreviations: APCs, Antigen-presenting cells; aPVs, Acellular pertussis vaccines; AVA, Anthrax vaccine absorbed; BN-OMVs, Bovine serum albumin nanoparticles; CaPNs, Calcium phosphate nanoparticles; cCHP, Cholesteryl group-bearing pullulan; CFs, Colonization factors; CPS, Capsular polysaccharide; CPTEG:CPH, 1,8-bis(p-carboxyphenoxy)−3,6-dioxaoctane: 1,6-bis(p-carboxyphenoxy)hexane; CRKP, Carbapenem-resistant *K. pneumoniae*; CSP, Circumsporozoite protein; CS-TPP, Chitosan-tripolyphosphate; CTB, Cholera toxin B subunit; CTL, Cytotoxic T cell; Cu-Zn SOD, Cu-Zn superoxide dismutase; DC, Dendritic cells; ETEC, Enterotoxigenic *E. coli*; EVs, Extracellular vesicles; FHV, Flock house virus; FUC, Fucoidan; GEM, Gram-positive enhancer matrix; GM1, Monosialotetrahexosylganglioside; HBV, Hepatitis B virus; HEC, Hectorite; Hib, Haemophilus influenzae type b; HIV, Human immunodeficiency virus; HPV, Human papillomavirus; HR, Heptad repeat; HTCC, N-(2-hydroxy)-propyl-3-trimethyl ammonium chitosan chloride; HUS, Hemolytic–uremic syndrome; LDH, 1,8-bis(p-carboxyphenoxy)−3,6-dioxaoctane: Hydroxide; ICG, indocyanine green; LEPS, Liposomal encapsulation of polysaccharides; LOS, Lipooligosaccharide; LPS, Lipopolysaccharides; LTA, Heat-labile enterotoxin A subunit; LTB, Heat-labile enterotoxin B subunit; MN, Microneedle; MSNs, magnetic mesoporous silica nanoparticles; NF, Nanofibrous membrane; N-IpaD, N-terminal region of IpaD; NMVs, Nano-multilamellar lipid vesicles; NP/NCMP, Poly (glycerol adipate-co-ω-pentadecalactone) (PGA-co-PDL) polymeric nanoparticles (NPs) / L-leucine microcarriers (nanocomposite microparticles-ncmps); OMVs, Outer membrane vesicles; PA, Protective antigen; PAD4, Domain 4 of PA; PAPE, Pickering emulsion; PBAE, Poly (β-amino ester); PLA, Poly (lactic acid); PLG, Poly (lactid-co-glycolid); PDNVs, protoplast-derived nanovesicles; PLGA, Polylactic-co-glycolic acid; PM, Pulmonary; PS-GAMP, Pulmonary surfactant-biomimetic liposomes; RBD, Receptor binding domain; RV, Rabies virus; SBA-15, Santa Barbara Amorphous-15; SEM, Scanning electron microscopy; stx, Shiga toxin; STING, Stimulator of interferon genes; STxA, Shiga toxin A subunit; Tfh, T-follicular helper; TLR, Toll-like receptor; TMC, Trimethyl chitosan; T_{RM}, Memory T cells; VLPs, Virus-like particles; wPV, whole-cell pertussis vaccine.

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1. Introduction

Epidemic infections, such as cholera, malaria, and the sudden outbreak of COVID-19, cause global life threats and socioeconomic recession. One of the most devastating pandemics was the Black Death, an infection caused by *Yersinia pestis*, which killed over 75 million people in 1350. At present, the world is still in the midst of the COVID-19 pandemic, with 3,398,302 COVID-19-related deaths recorded as of May 19, 2021 (https://covid19.who.int/). Furthermore, antibiotic resistance leads to the ineffectiveness of traditional antibacterial treatments, and nearly half a million new cases of multidrug-resistant tuberculosis (MDR-TB) occur worldwide [1].

Among coping strategies for emerging infectious diseases, preventive vaccination is a crucial strategy [2] and the only one with wide and thorough effects on the public health. For example, since 2000, vaccination has reduced the reported incidence of measles by 83%, thereby preventing over 20 million deaths [3]. Vaccines work by training and utilizing the body's immune system to recognize and fight the pathogens. However, the high infection rates, widespread transmission, or high fatal ratio of certain epidemic germs raised huge challenges for the design of prophylactic vaccines.

Vaccines have evolved from the live-attenuated or inactivated vaccines to the subunit/peptide vaccines. Regardless of the safety issues, the live-attenuated and inactivated vaccines, which are nanoparticles themselves [2], are ready to be captured and processed by antigen-presenting cells (APCs), including dendritic cells (DCs), macrophages, and B cells, resulting in an efficient immune response. In contrast, subunit vaccines or recombinant vaccines are characterized by improved safety, but much weaker immunogenicity. To break the bottleneck of previous vaccine types, advanced delivery systems (e.g., micro/nano delivery) exhibiting both high efficacy and safety are greatly required. Such systems will likely help to catalyze novel candidate vaccines toward clinical testing at an unprecedented speed. For example, lipid nanoparticles dictated the success of the mRNA vaccines in 2020, making an enormous contribution to control the spread of COVID-19 at a global level.

The advantages of vaccine delivery systems have been well documented in recent reviews. For example, Ding et al. [4] summarized the nanosystems with superior therapeutic or preventive effects, providing an important clue on maintenance of our well-being by exploiting the immunomodulatory property of nanomaterials. Other works also referred to using nanotechnology or materials science approaches with delivery systems [5,6]. In addition, vaccine delivery systems focusing on tackling a particular infectious disease (e.g., COVID-19) [7] or cancer [8] were reviewed. Nevertheless, there has been no systematic summary of advanced delivery systems and design concepts for prophylactic vaccines for a wide range of epidemic infectious diseases. Taking into account the diverse species and pathogenic mechanisms of infection pathogens, the protection efficacy of different systems against the same infection has not been sufficiently compared. In addition, the requirements and priorities of the delivery systems for different infectious diseases or stages are also case by case. Obtaining such data would greatly support designing the optimal delivery vectors for specific infectious diseases.

In this review, we provide an overview of the major or epidemic infectious diseases (pneumonia, diarrhea, candidiasis, malaria, and others) caused by bacteria, viruses, fungi, and parasites. We also list advanced delivery systems against different infectious diseases and compare their protective efficacy from different aspects. Moreover, we include the current vaccines and vaccine delivery systems that are either newly licensed (e.g., COVID-19 vaccines) or close to licensure. In particular, we highlight the advanced delivery systems with high efficiency, cross-protection, or long-term protection against epidemic pathogens.

2. Bacterial infectious diseases and advanced delivery systems

2.1. Respiratory infectious diseases and advanced delivery systems

Respiratory infections represent a serious health problem worldwide that mainly affects children, older people, and immunocompromised individuals. Pneumonia vaccines (e.g., 23-valent polysaccharide vaccines, 13-valent polysaccharide conjugate vaccines) have achieved great success worldwide. Nevertheless, the existence of a variety of serotypes (>95) of *S. pneumoniae* makes the capsular polysaccharide (CPS)-based vaccines unable to provide broad protection [9], while the cost of preparing vaccines containing all serotypes is very high. In addition, there may still be undetected serotypes [10]. In this case, effective delivery systems of proteinaceous antigens have been developed for the prevention of pneumonia. In addition to the delivery efficacy, a combined mucosal and systemic immune response is also appreciated for pneumonia vaccines [11], which not only requires novel delivery design but also a specific administration route (e.g., noninvasive mucosal routes). At present, there are a variety of delivery systems for pulmonary infectious diseases and they have shown good results (Table 1).

2.1.1. S. pneumoniae

S. pneumoniae is a global endemic pathogen causing a wide range of clinical diseases, such as pneumonia, meningitis, and sepsis, which frequently lead to death among children all over the world, especially in developing countries [46]. Colonization with *S. pneumoniae* in humans is universal [47]; however, it provides an opportunity for the remaining serotypes to establish residence and progress to virulence [48,49]. In addition to direct infection, the bacteria usually exist in the form of biofilm, and some destructive events, such as viral infection, can prompt the release of a virulent subpopulation of bacteria to the lungs, blood, middle ear, and other parts of the body, causing the aforementioned diseases [50,51]. Therefore, high levels of IgG antibodies produced by humoral immunity are very important for invasive infections, and antigen-specific sIgA antibodies are the key to prevention of *S. pneumoniae* colonization of the upper respiratory tract.

Various delivery vehicles (e.g., polymers, virus-like particles (VLPs), *L. lactis*, liposomes) have been used to deliver *S. pneumoniae* protein or glycan antigens, which showed a strong ability to prevent bacterial invasive infections and inhibit the colonization of the respiratory tract (Table 1). Among them, some vaccine formulations offered universal pneumococcal disease prevention. For example, Jones et al. proposed a vaccine platform through the liposomal encapsulation of polysaccharides (LEPS) technology. The completed LEPS vehicle (about 300 nm in size) was coupled with the PncO and GlpO protein antigens (identified through an antigen discovery and validation model that selectively targeted pneumococci virulence transition [52]) for the liposomal containment of polysaccharides (serotypes 19F, 11A, and 35C). Thus, this vaccine not only prevents the colonization of the most aggressive *S. pneumoniae* serotypes, but it also restricts virulence transition [15]. Since pneumonia vaccines are often used in children and older adults, the safety and immune activation ability of the delivery carriers need to be greater. Thus, we further focused on the latest several delivery systems that can produce the best protective effect.

Nanogel It has been reported that a self-assembled nanosized hydrogel (nanogel) containing a cationic type of cholesteryl group-bearing pullulan (cCHP) can be used as a vaccine delivery system [53–55]. This nanogel could effectively transfer antigen to nasal epithelial cells and dendritic cells (DC) under the basement membrane and induce antigen-specific immune response as a non-adjuvanted vaccine (Fig. 1). After loading with a single protein antigen PspA, both specific IgG levels in the serum and bronchial fluids and IgA levels in the nasal fluid were significantly elevated in nasally administered mice [12], and all of the responses were involved in establishing protective immunity against pneumococci [56–59]. Further, a study in rhesus macaques revealed that the cCHP-based pneumococcal vaccine induced significantly elevated PspA-specific IgG and IgA levels and kept them for a long time [60]. Moreover, positron emission tomography (PET) analysis combined with magnetic resonance imaging (MRI) has confirmed that the cCHP nanogel vaccine is not deposited in the olfactory bulbs and brains in macaques [60], suggesting that it is also safe to use as a nasal vaccine in humans.

Hybrid biological-biomaterial vector Yi et al. have reported a combined delivery device named hybrid biological-biomaterial vector, which consists of a bacterial core electrostatically coated with a cationic polymer (a mannosylated poly (β-amino ester) (PBAE)) [62]. The biological portion of the vector is a bacterial cell (live or dead), containing natural adjuvant properties, and it is beneficial for passive targeting of phagocytic APCs (Fig. 2). The vector's composition and the surface characteristics endowed by the mannosylated PBAE engage APC receptors and enhance the uptake upon vector administration. After subcutaneous injection of the vector expressing pneumonia PspA protein antigen in mice, a strong specific immune response providing a wide range of protection against 10 different clinical *S. pneumoniae* was induced. Moreover, the localization of PspA in the cytoplasm could provide a stronger immune protection effect than that in the periplasm or on the surface of bacteria [13]. As for the combination of biomaterial and biological components, each has its own antigen delivery characteristics and plays a role in the immune process. Moreover, such synergy is conducive for obtaining the best immune effects. In addition, *E. coli* can be further modified by genetic engineering to be more suitable for antigen delivery. Because the antigen is loaded with bacterial vectors, it provides a variety of possibilities for using different antigen locations and different loading forms, such as proteins and nucleic acids.

2.1.2. Klebsiella pneumoniae

K. pneumoniae belongs to gram-negative family *Enterobacteriaceae*. It exists widely in the natural environment and acts as opportunistic pathogen, so serious infections may be induced in patients with severe infections and weakened immune system [63]. *Klebsiella* species remain the world's most common nosocomial pathogens [64] and the main cause of hospital-acquired pneumonia resulting in high mortality rate. Currently, the biggest challenge of *K. pneumoniae* treatment is drug resistance, which makes the use of common antibiotics ineffective. Indeed, the extended-spectrum β-lactam-producing and carbapenem-resistant *K. pneumoniae* (CRKP) has been recognized by the World Health Organization as a critical public health threat [65].

Outer membrane vesicles (OMVs) A large number of gram-negative bacteria can naturally produce extracellular OMVs, which have significant advantages in vaccine development. Compared with other lipid nanoparticles, OMVs contain toll-like receptor (TLR) agonists, such as outer membrane proteins, lipoproteins and lipopolysaccharides (LPS), and a variety of immunogenic endogenous antigens. Generally, the diameter range of OMVs is from 50 nm to 250 nm, which is suitable for targeting and being phagocytized by APCs [66]. The use of OMVs has become a very promising strategy of vaccination. *K. pneumoniae*-derived OMVs can induce strong humoral and cellular immunity response, preventing bacteria-induced lethality in intraperitoneally immunized mice [31]. Although natural OMVs are considered potential vaccine candidates, they have some shortcomings. One is a wide size range of OMVs naturally secreted by bacteria, which may complicate the vaccine dynamics *in vivo*, and the low stability of natural OMVs

Table 1
Effect of vaccines with delivery systems against pulmonary infectious diseases.

Pathogenic bacteria	Delivery system	Antigen(s)	Adjuvants used	Route	Animal species	Protection after challenge	Ref.
S. pneumoniae	cCHP Nanogel	PspA	—	i.n.	Mice	100% of animals surviving	[12]
	Hybrid biological-biomaterial vector (PBAE and bacterial core)	PspA or PspA[b]	—	s.c.	Mice	100% of animals surviving	[13]
	Liposomes	Polysaccharide (Serotypes 3)	—	i.n.	Mice	No results	[14]
	LEPS	PncO, GlpO, and polysaccharide (Serotypes 19F, 11A, and 35C)	—	s.c.	Mice	100% of animals surviving	[15]
	Chitosan	PsaA	—	i.n.	Mice	100% of animals surviving	[16]
	Chitosan	PsaA (DNA)	—	i.n.	Mice	Decreased bacterial colonization in nasopharynx	[17]
	Polyanhydride nanoparticles	PspA	—	s.c.	Mice	No results	[18]
	PLA microparticles	PspA	—	i.m.	Mice	No results	[19]
	NP/NCMP	PspA4Pro	—	PM	Mice	67% of animals surviving	[20]
	L. lactis, *L. casei*, *L. plantarum*, and *L. helveticus*	PsaA (Surface)[b]	—	i.n.	Mice	Decreased bacterial colonization in the nasal mucosa	[21]
	L. casei	PspA[b]	—	i.n.	Mice	33% of animals surviving	[22]
	L. casei	PspA5 (Cytoplasm)[b] or PspC (Cytoplasm)[b]	—		Mice	PspA5: 40% of animals surviving; PspC: 20% of animals surviving	[23]
	L. casei	PspC (Surface or Cytoplasm)[b]	—	i.n.	Mice	Decreased bacterial colonization in the nasopharynx	[24]
	L. lactis	PspA[b]	—	i.n.	Mice	40% of animals surviving	[25]
	L. lactis	PppA[b]	—	i.n.	Mice	60% of adults and 70% of young mice surviving	[26]
	L. lactis (GEM) or live *L. lactis*	PppA or PppA[b]	—	i.n. or oral	Mice	Decreased bacterial number in the lungs and blood	[27]
	L. lactis (GEM)	IgA1p, PpmA, and SlrA	—	i.n.	Mice	Decreased bacterial number in the lungs, blood, and nose from trivalent vaccine and the divalent formulation containing SlrA and IgA1p	[28]
	VLP (Qβ)	TS3 and TS14 (chemically synthesized two kinds of capsular polysaccharides repeated units)	—	i.m.	Mice	TS14: 90% of animals surviving, compared with 66% of controls; TS3: 95% of animals surviving, compared with 40% of controls	[29]
	VLP (HBsAg)	Capsular polysaccharide 33F	—	s.c.	Mice	No results	[30]
K. pneumoniae	OMVs	OMV components	—	i.p.	Mice	100% of animals surviving	[31]
	BN-OMVs	OMV components	—	s.c.	Mice	100% of animals surviving	[32]
	Alginate microparticles	LPS of *K. pneumoniae* O1 serotype	—	i.m., i.t.[a], or i.n.	Mice	Decreased bacterial loading in the lungs	[33]
B. pertussis	OMVs	OMV components	—	i.p. or i.n.[a]	Mice	Decreased bacterial colonization in the lungs	[34]
	OMVs	OMV components	—	s.c.	Mice	Decrease bacterial colonization in the lungs; slightly faster than that of wPV	
	OMVs	OMV components	—	PM[a] or s.c.	Mice	Decreased bacterial colonization in the lungs, trachea, and nose	[35]
	OMVs deriving from *B. parapertussis*	OMV components	—	i.p.	Mice	Cross-protection	[36]
	Lipid A-modified OMVs	OMV components	—	i.n.	Mice	Decreased bacterial counts in the lungs	[37]
	L. acid bacteria (GEM)	PTd, FHA, and PRN	—	i.p. or i.n.[a]	Mice	Decreased bacterial counts in the lungs and trachea (but not reaching statistical significance compared with antigen alone)	[38]
	PLGA nano/microparticle	PTd	—	s.c.	Mice	Decreased bacterial counts in the lungs	[39]
	PLG nano or microparticle	PTd and FHA	—	Oral, i.p.[a], i.m.[a], or s.c.	Mice	Decrease bacterial counts in the lungs	[40]
Haemophilus influenzae type b (Hib)	Chitosan hydrogel (ViscoGel)	a commercial Hib conjugate vaccine (Act-Hib)	—	s.c. or i.m.	Mice	No results	[41]
	VLP (HBsAg)	PRP polysaccharide	—	s.c.	Mice	No results	[42]
Mycobacterium tuberculosis	Chitosan	Esat-6 three T cell epitopes (Esat-6/3e) and fms-like tyrosine kinase 3 ligand (FL) genes (DNA)	—	i.m. prime (Esat-6/3e-FL) and i.n. boost (Esat-6/3e)	Mice	Decreased bacterial counts in the lungs and spleens	[43]
	Chitosan	Mycobacterium lipids	—	i.p.	Mice	No results	[44]
Mycobacterium bovis	Liposome	Fusion of antigen 85b and Esat-6	—	s.c.	Mice	Decreased bacterial counts in the lungs and spleen	[45]

a. The better or the best route to achieve protection; b. Constructed in an expression vector; i.n., intranasal; s.c., subcutaneous; i.m., intramuscular; i.p., intraperitoneal; i.t., intratracheal; PM, pulmonary; —, without added adjuvant.

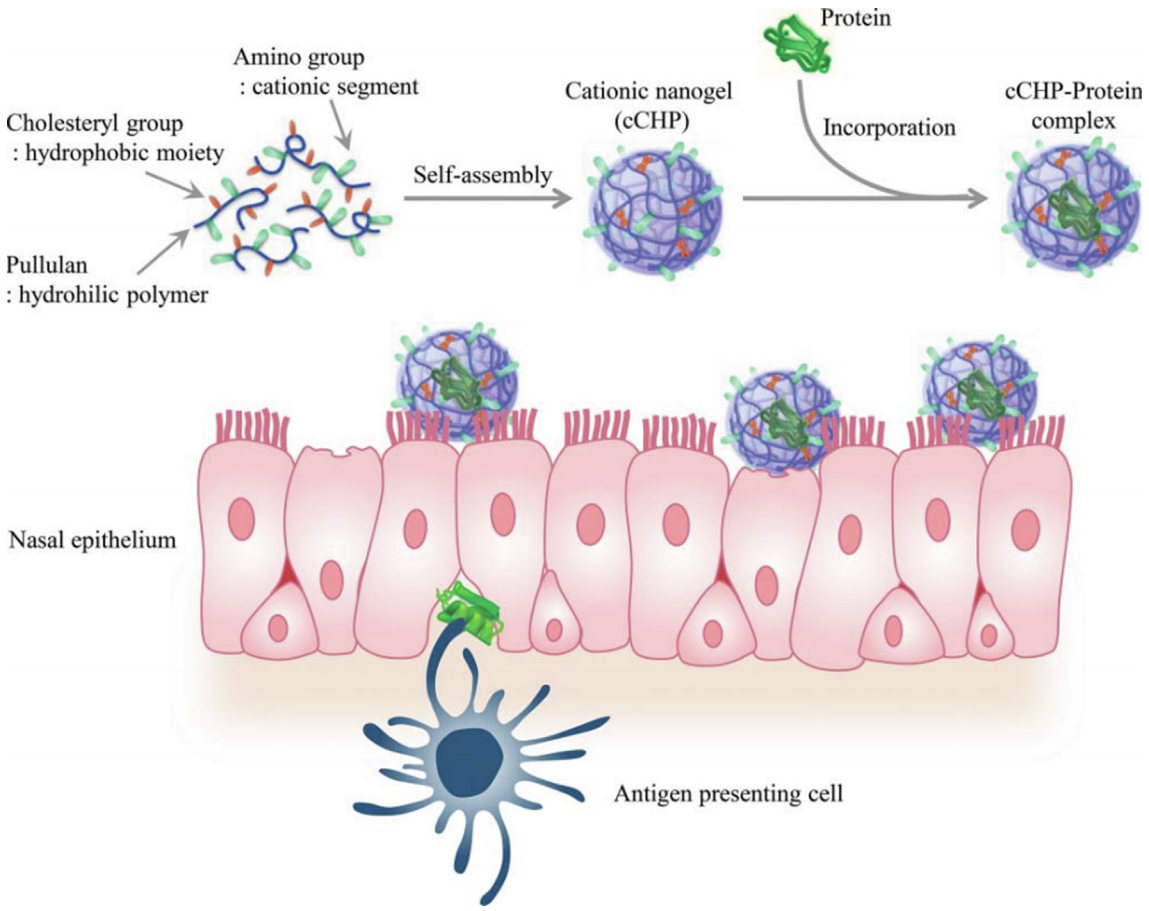

Fig. 1. Application of cCHP nanogel as nasal immune delivery system via nasal route [61]**.** cCHP is composed of a cholesteryl group-bearing pullulan (CHP) with a cationic amino group. cCHP nanogels can encapsulate proteins in the internal space through hydrophobic interactions and effectively retain them in the negatively charged nasal mucosa.

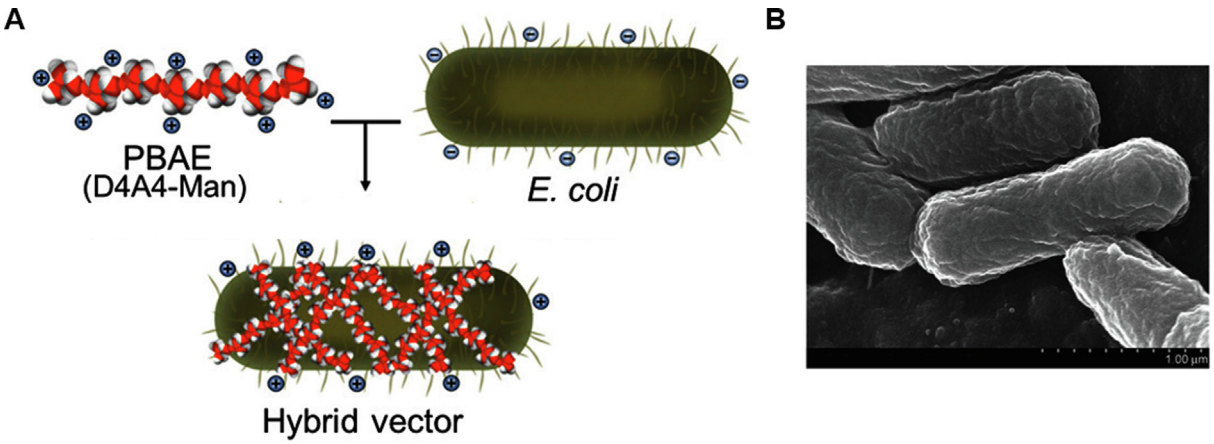

Fig. 2. Construction of a hybrid biological-biomaterial vector [62]**.** (A) Schematic diagram of the hybrid biological-biomaterial vector preparation. (B) Scanning electron microscopy image of the vector.

also profoundly affects the vaccine effect. To solve these problems, Wu et al. described a core-shell structure to reinforce the OMVs by depositing the hollow-structured OMVs onto bovine serum albumin nanoparticles (BN-OMVs). The size of the BN-OMVs was mostly between 70 and 90 nm, and the immune response and protection against CRKP were significantly improved after subcutaneous vaccination [32].

Alginate microparticles Microcapsules have been developed as a delivery vector for mucosal vaccines because they could improve the uptake into APCs and sustain the release of antigenic material**.** As polymers, alginate microparticles are easy to obtain and inexpensive and have several advantages in vaccines. Unlike the formation of (lactide-co-glycolide) PLG particles, which require harsh denaturation conditions, the conditions for alginate microparticles

formation are mild [67]. Moreover, the mucoadhesive properties of alginate microparticles may prolong the contact time with the absorptive epithelium and the mucosa-associated lymphoid tissue M cells, thus promoting the uptake of the coated antigen. When LPS of *K. pneumoniae* O1 was loaded in alginate microparticles, the particle size was less than 5 μm. Both effective systemic and mucosal immune responses were induced following nasal and inhalation administration, which protected rodents against lobar pneumonia [33]. Although LPS encapsulation with microspheres or liposomes can reduce its pyrogenic and toxic properties and induce protective polysaccharide antibody [68], the natural LPS can still cause severe inflammation. At present, many serotypes of *K. pneumoniae* have been identified, but only four of them (O1, O2, O3, and O5) can cause human diseases, indicating that O-polysaccharide-based vaccines could provide a high coverage. However, the O-polysaccharide has high specificity but low immunogenicity, which requires more efficient delivery systems.

2.1.3. Bordetella pertussis

Pertussis is a serious childhood respiratory disease, with the main feature of a persistent and paroxysmal cough, accompanied by a typical inhalation "whooping" sound. A typical pertussis infection usually lasts 3 months. Therefore, it is also called "hundred-day cough" [69]. The disease is caused by *B. pertussis,* which mainly spreads through aerosols and may settle in the respiratory tract, thereby damaging epithelial cells and impairing normal respiratory function. Although acellular pertussis vaccines (aPVs) containing multiple antigen components can provide wider coverage [70], there are still problems to be solved, such as poor immunization response and short-term protection. In addition, surveys in many countries have found that the incidence of pertussis is increasing, and there have even been pertussis outbreaks in many countries and regions in recent years [71–73]. This phenomenon is also known as the "Pertussis Resurgence" [74,75]. Therefore, pertussis still poses a threat to the health of children, and a safer and more protective vaccine is needed.

Many delivery vehicles, such as OMVs, *L. acid* bacteria, and polymers have been developed against *B. pertussis.* Among them, OMVs have been most thoroughly studied. Many studies have demonstrated that OMVs derived from *B. pertussis* can protect mice from intranasal pertussis challenge through different immune routes, including intraperitoneal, subcutaneous, intranasal, and pulmonary (PM) [34,35,76]. The classical administration route of OMVs is subcutaneous or intraperitoneal, which does not cause an IgA reaction [77]. For respiratory diseases, mucosal immunity seems more important. By comparing the immune responses evoked by the PM and subcutaneous route, a distinct systemic and a stronger mucosal IgA and Th17 immune response were observed with PM immunization; the PM route also provided more effective inhibition of bacterial colonization in the respiratory tract [35]. Thus, mucosal immunization may be of great significance to improve protection against *pertussis* infection. Although the systemic proinflammatory cytokine responses have been greatly reduced compared with the whole-cell pertussis vaccine (wPV) [76], a further detoxification is necessary considering that native *B. pertussis* OMVs contain a lot of lipooligosaccharide (LOS), which could induce strong host inflammatory responses. Asensio et al. developed a recombinant *B. pertussis* strain expressing the lipid A-modifying enzyme, PagL, which hydrolyzes the ester bond at the 3 position of lipid A, resulting in tetra- instead of penta-acylated LOS. The OMVs derived from the recombinant strain retained protective capacity against intranasal challenge in intranasally immunized mice [37]. In addition, a cross-protection study found that OMVs derived from *B. parapertussis*, a close relative of *B. pertussis* that can also cause pertussis, could provide protection from both *B. pertussis* and *B. parapertussis* infections [36]. Further, long-term protection from pertussis OMV-based vaccine is based on the induction of lung-resident $CD4^+$ memory T cells (T_{RM}) [78], suggesting that effectiveness may cover the entire period of childhood.

Respiratory pathogenic bacterial infections involve colonization and invasion; therefore, mucosal immunity is considered an ideal choice for the prevention of respiratory diseases and blocking transmission because it involves both mucosal and humoral immune responses. Nasal mucosal immunity has the advantages of low response threshold, low antigen dosage, and no immune tolerance. However, under conventional conditions, antigens can only stay on the mucosal surface for a short time after entering the nasal cavity, and a small amount of proteolytic enzymes and mucus weaken the strength of the immune response. Therefore, the main requirement for a nasal mucosal immune delivery system is to enhance the adhesion and retention of antigens on the mucosal surface, enhance the immunogenicity of the antigens, and promote the effective uptake of antigens by DCs.

In addition, polysaccharide antigens have strong specificity, and the produced antibodies are protective. The polysaccharide conjugate vaccine for *S. pneumoniae* has achieved great success. However, the current chemical preparation method is a time-consuming and multistep process, which makes the vaccine expensive and difficult to popularize in developing countries. In contrast, the current biotechnology of coupled bacterial polysaccharide and carrier protein based on protein glycosylation modification has achieved partial success and is expected to overcome the limitations of polysaccharide conjugate vaccine. The use of VLP to couple a single polysaccharide repeat unit of *S. pneumoniae* can also produce a protective effect, suggesting that nanocarriers have advantages in stimulating polysaccharide immune responses. Therefore, the combination of a nanodelivery carrier and glycosylation system is expected to prepare a new, low-cost, high-efficiency pneumonia polysaccharide conjugate vaccine. Although a variety of probiotic carriers were used in the research of pneumococcal vaccines, the final immune effect was not optimal. It may be that, compared with the intestine, the respiratory environment is not suitable for their survival, colonization, presentation, and antigen release. In addition, about 80% of clinical isolates of *K. pneumoniae* belong to one of four serotypes (O1, O2, O3, and O5), so polysaccharide antigens can be used to prepare multivalent vaccines. However, the immunogenicity of OPS is generally low, especially for O2 polysaccharide repeat units composed of two simple galactoses, which makes it difficult for O2 antigen to stimulate an effective immune response using traditional vaccine strategies. Therefore, delivery systems for weak polysaccharide antigens need further development.

2.2. Intestinal infectious diseases and advanced delivery systems

Diarrhea, mainly manifested as watery and loose stools many times a day, is a major global health problem [79]. Bacterial diarrhea, specifically, is a more serious condition with severe symptoms. The most common microorganisms that cause bacterial diarrhea are *Escherichia coli*, *Shigella*, *Salmonella*, *Yersinia,* and *Clostridium* [80]. In bacterial diarrhea, pathogens attach to the epithelium, produce toxins, and increase intracellular cAMP or cGMP, ultimately accelerating the secretion process in the enterocytes [81]. Toxins may also induce the release of cytokines, leading to chemotaxis and eicosapentaenoic acid (prostaglandin) production, and aggravate the imbalance of water in the lumen. Excessive water and electrolytes in the intestinal cavity draw more fluid into the intestinal cavity, and the osmotic effect further worsens diarrhea [82]. Therefore, inhibiting bacterial colonization in the intestine can effectively prevent infection, and this ability often comes from IgA produced by mucosal immune response. It is an ideal

way for antigens to directly act on the intestinal mucosal immune system to stimulate mucosal immune response. In addition, due to the higher safety of oral administration, some inorganic carriers have also been explored. However, unlike respiratory delivery, most vaccines need to overcome various difficulties to reach the intestinal tract, such as resistance to gastric acid and bile, ability to colonize the intestinal tract, and possible immune tolerance. The delivery systems for the prevention of bacterial diarrhea are summarized in Table 2.

2.2.1. Pathogenic E. coli

Enterotoxigenic *E. coli* (ETEC) is the most common cause of diarrhea in humans [81]. It has become a major global food and waterborne pathogen involved in outbreaks of bloody diarrhea and hemolytic–uremic syndrome (HUS) worldwide [122]. Colonization factors (CFs), produced in ETEC, were considered as targets for vaccine production [123,124]. Although about 25 different types of CFs have been identified [123,125], naked CFs are not suitable for oral immunization because of their high sensitivity to the harsh environment of the gastrointestinal tract.

Lactic acid bacteria Lactic acid bacteria are a safe and efficient mucosal delivery carrier, which is widely used in the prevention of gastrointestinal infectious diseases. Compared with some other carriers, lactic acid bacteria are more favorable for oral administration because they can pass through the extreme environment of the stomach and colonize the intestine. Moreover, both strong antigen-specific systemic and mucosal immune responses are induced by lactic acid bacteria through mucosal immunity. In the design of *E. coli* vaccine, antigens could be located on the surface, in the cytoplasm, or be secretions of lactic acid bacteria (Fig. 3). At present, many lactic acid bacteria, such as *L. reuteri*, *L. casei*, *L. plantarum*, and *L. plantarum,* have been used to express a variety of antigens, but *L. casei* has been most studied [126]. For example, *L. casei* expressing F41 constructed by Liu et al. can stimulate strong systemic and local mucosal immune responses simultaneously after oral immunization, protecting mice from lethal challenge. It is worth noting that this immunization strategy can also stimulate long-term protection, considering that it can maintain more than 80% protection 9 weeks after the last immunization [84,85]. Another study also revealed the passive protection effects of *L. casei* expressing F41 antigen considering that the orally or intranasally immunized dams provided 90% protection against lethal challenge to their offspring [86]. Furthermore, Yu et al. found that immunization with *L. casei* co-expression or fusion expression of FaeG antigen and fusion protein (including LTB and mutated LTA) can stimulate a stronger mucosal immune response and provide 100% protection [89]. Since the intestinal epithelium contains a large number of M cells, which can bind B5 toxins (such as LTB and CTB) through the GM1 receptor [127], B5 toxin proteins can be used as a mucosal adjuvant to further improve the mucosal immune response of the lactic acid bacteria-based delivery system.

OMV OMVs have been widely studied for the use in vaccines. Intranasal immunization with OMVs from ETEC was shown to induce antibodies against various virulence proteins and inhibit bacterial colonization in the small intestine [128]. However, due to the existence of shiga toxin (STx) and LPS endotoxins, the OMVs produced from EHEC O157: H7 have intrinsic toxicity with the possibility to develop HUS; thus, the preparation of *E. coli* O157: H7 OMV vaccine needs to overcome its toxicity. Kim et al. generated attenuated OMVs through the mutation of *msbB* (encoding an acyltransferase that catalyzes the final myristoylation step during lipid A biosynthesis) and A subunit of STx [129,130]; after immunizing mice by eyedrops and confirming the safety, both humoral response and mucosal (in tears, saliva, and feces) immune response were induced, providing enough protection from the challenge by the lethal HUS-causative agent (wild-type OMVs) [94]. Although there is relatively poor lymphoid tissue in the eyes and there are a few reports on immunization via eyedrop route, the connection of lacrimal duct and nasal cavity may result in immunoactivities in both nasal and ocular mucosa. Moreover, the homing of lymphocytes can distribute the effect of mucosal immune response on each mucosal surface of the body; therefore, the intestinal IgA can be successfully induced through other mucosal pathways. Considering that the response at the immune location is still the strongest, the oral route of OMVs should be further tried.

Compared with the application of OMVs-based vaccines in the prevention of respiratory diseases, OMVs delivery systems have more applications in intestinal diseases, and correspondingly, there are a series of successful modifications to OMVs. First, various methods can reduce the toxicity of OMV. The toxicity of OMVs can be reduced by deleting the lipid A modification gene *msbB, htrB*, or combined *msbB* and *pagP* [131–134]. Another method to reduce the toxicity of OMVs is to pre-treat them with all-trans retinoic acid, active metabolite of vitamin A, which has both anti-inflammatory and mucosal adjuvant properties [135]. Then, through some modifications, the OMV yield can be improved. Choi et al. produced OmpC-enriched OMVs through overexpression of small RNAs, MicA, in *S. typhimurium*. The yield of OMVs was strongly increased and the OmpC-enriched OMVs promoted Th1- and Th17-type immune responses, providing full protection against lethal challenge by *Salmonella* [136]. Furthermore, the yield can also be improved through the deletion of *tolR* gene to disrupt the Tol-Pal system on the cell wall. After immunization through the subcutaneous route, the protective effects of OMVs in mice were not inferior compared with those of polysaccharide conjugate vaccines [137]. In addition, by further optimizing the form of OMVs, immune response and protection can be additionally improved, namely, OMVs encapsulated in polyanhydride nanoparticles (OMV-NPs) can induce Th1 immune responses [109,138], which is more suitable for intracellular bacteria, such as *S. flexneri*. The OMV-NPs formulation even provided full protection on day 56 after nasal immunization in mice, while the protection with OMVs alone was only 40% [108]. Thus, OMVs, which are easier to produce, have a great potential to become a candidate product for the application of vaccines against intestinal infectious diseases.

Eudragit L-100/Chitosan Chitosan is a natural biodegradable polysaccharide derived from chitin, with good biocompatibility and adhesion properties. Although chitosan is capable of increasing transit time of antigens in the gastrointestinal tract and inducing mucosal immune response, its oral administration is limited by the low resistance to acidic pH [139,140]. To solve this problem, Eudragit L-100, a coating material soluble at pH above 6.0, was used to protect the antigens from detrimental effects in the upper gastrointestinal tract. As reported, Eudragit L-100-based oral delivery vehicle loading ETEC F4 or F18 antigen could induce higher antigen-specific IgG1 and IgG2a antibody responses in serum and antigen-specific IgA in saliva compared with those with antigen immunization alone [141]. To further improve the immune response, a combined delivery system was built by coating Eudragit L-100 on the chitosan nanoparticles which loaded protein antigens or OMVs from ETEC. Oral immunization of the formulations in animals elicited antibody response and inhibited the ETEC colonization in small intestine [95,96]. Thus, for some special delivery requirements, multiple delivery strategies can be used at the same time.

In addition to the vehicles described above, some other polymers, inorganic materials, and lipid or oil-based vehicles have been explored to develop *E. coli* vaccines (Table 2). Although strong immune response could be elicited in mice, most of the results lack the *in vivo* results about the protective effect, and therefore further confirmation is needed.

Table 2
Effect of vaccines with delivery systems against intestinal infectious diseases.

Pathogenic bacteria	Delivery system	Antigen(s)	Adjuvants used	Route	Animal species	Protection after challenge	Ref.
E. coli	*L. reuteri*	Fusion of ST and LTB[b]	—	Oral	Mice	Decreased gut/carcass weight (G/C) ratios	[83]
	L. casei	F41 or K99 fimbriae (Surface)[b]	—	Oral or i.n.	Mice	Over 80% of animals surviving with a high dose, 9 weeks after the last immunization; Passive protection (F41 fimbriae): 90% of pups surviving, oral; 80% of pups surviving, i.n.	[84–86]
	L. casei	β-Intimin fragment[b]	—	Oral or s.l.	Mice	Decreased bacterial recovery from feces	[87]
	L. casei	Fusion of K99, K88 fimbriae (Surface)[b]	fuse expressing LTB	Oral	Mice	Over 80% of animals surviving 3 weeks after the last immunization, and over 70% of animals surviving 9 weeks after the last immunization	[88]
	L. casei	FaeG[b]	co-expressing or fuse expressing mutated LTA and LTB	Oral	Mice	100% of animals surviving	[89]
	L. plantarum	FaeG with DC-targeting peptide[b]	—	Oral	Mice	Inflammation of intestinal tissue prevented	[90]
	L. acidophilus	EspA and the Tir central domain (Secreted)[b]	—	Oral	Mice	80% of animals surviving	[91]
	L. acidophilus	K99 (Surface)[b]	—	No results	Pigs	No results	[92]
	L. reuteri	PapG (Surface)[b]	—	No results		No results	[93]
	Detoxified OMVs	OMV components	—	Eyedrop	Mice	100% of animals surviving, compared with 20% of controls	[94]
	Chitosan + Eudragit L-100	F4 fimbriae	—	Oral		Reduction in excretion of bacteria	[95]
	Chitosan + Eudragit L-100 + OMVs	OMV components	—	Oral	Mice	No results	[96]
	PLGA	CS3, CS1, LTB, and chimeric CFA/I, CS2, CS3, and LTB	—	Oral, s.c., or i.p.	Mice	No results	[97,98]
	PLG microspheres	CS6	—	i.n.	Mice	No results	[99]
	Nano-multilamellar lipid vesicles (NMVs)	Stx2B	—	s.c.	Mice	60% of animals surviving	[100]
	Oil-based Vaxcine™	Conjugation of O111 polysaccharide and EtxB	—	Oral	Rabbits and mice	No results	[101]
	LDH and HEC nanoparticles	IB	—	s.c.	Mice	No results	[102]
	SBA-15	Int1b or O-polysaccharides	—	s.c.	Rabbits and mice	No results	[101,103]
Shigella	OMVs of six strains		—	Oral	Mice	Neonatal mice were 100% passively protected against *S. flexneri* 2a and *S. flexneri 6*, while the protective efficacies against *S. dysenteriae 1*, *S. flexneri 3a*, *S. boydii 2,* and *S. sonnei* were ~90%	[104]
	Detoxified OMVs	OMV components	Alhydrogel	i.n., i.d., s.c., i.p., or i.m.	Mice, rabbitsand human	No results	[105–107]
	OMVs or OMVs encapsulated in polyanhydride nanoparticles (OMV-NP)	OMV components	—	i.d., i.n., eyedrop, or oral	Mice	OMVs: 100% of animals surviving by nasal and ocular route, and no animal surviving by intradermal route; OMV-NP: 100% of animals surviving by the nasal, oral, and intradermal route	[108,109]
	OMVs encapsulated in CS-TPP particles and Eudragit L-100	OMV components	—	Oral or i.d.	Mice	passive immunity protection	[110]
	Self-assembled proteinaceous nanoparticles	O-polysaccharide	—	s.c.	Mice	100% of animals surviving	[111]
	Chitosan	MxiH	—	i.n.	Mice	60% of animals surviving, compared with 10% of controls	[112]
	Chitosan NF	N-IpaD	—	i.n.	Guinea pigs	93.75% protective efficacy against ocular challenge in guinea pigs	[113]

Table 2 (*continued*)

Pathogenic bacteria	Delivery system	Antigen(s)	Adjuvants used	Route	Animal species	Protection after challenge	Ref.
	TMC nanoparticles	N-IpaD	—	Oral	Guinea pigs	83.3% protection against ocular challenge in guinea pigs	[114]
V. cholerae	OMVs	OMV components	—	Oral, i.n., or i.p.	Rabbits and mice	60%–100% protective from watery diarrhea from different *V. cholerae* strains in rabbit; 100% protection against colonization with *V. cholerae* in neonatal mice from immunized dams	[115,116]
	L. casei or *L. reuteri*	CTB (Cytoplasm or secretory)[b]	—	No results	Mice	No results	[117]
S. typhimurium	OMVs	OMV components	—	i.p.	Mice	Bacterial replication inhibited	[118]
S. typhi and *paratyphi* A	Bivalent OMVs	OMV components	—	Oral	Mice	80% of animals surviving against *S. typhi* and 90% of animals surviving against *S. paratyphi* A	[119]
S. typhi	VLP (HBsAg)	Vi	—	s.c.	Mice	No results	[42]
S. enterica serovar Enteritidis	*L. casei*	FliC (Surface)[b]	—	Oral	Mice	Decreased bacterial counts in the spleen	[120]
S. enterica serovar Enteritidis	*L. casei*	FliC (Surface)[b] or fusion of FilC and SipC (Surface)[b]	—	No results	Mice	No results	[121]

b. Constructed in an expression vector; i.n., intranasal; s.c., subcutaneous; i.m., intramuscular; i.p., intraperitoneal; i.d., intradermal; s.l., sublingual; —, without added adjuvant.

2.2.2. Shigella

Shigella species are gram-negative bacteria belonging to the *Enterobacteriaceae* family. According to the serological type, they are divided into four categories: *S. dysenteriae*, *S. boydii*, *S. flexneri*, and *S. sonnei*. *Shigella* spp. are the main bacterial causes of persistent epidemic diarrhea and result in almost 125 million diarrheal episodes and around 160,000 deaths annually [142]. Usually, a low-dose inoculum can cause the disease, resulting in aggressive watery or mucous/bloody diarrhea. However, there is currently no licensed vaccine against *Shigella*, and the continuous emergence of drug-resistant strains makes antibiotic treatment difficult [143].

Self-assembled proteinaceous nanoparticles Recently, Pan et al. developed Nano-B5 platform to produce nanoscale bacterial polysaccharide conjugate vaccines *in vivo*. Proteinaceous nanoparticles were self-assembled via fusion of a natural adjuvant effective pentamer domain (bacterial B5 toxin) and an unnatural trimer domain. Then, O-polysaccharide of *S. flexneri* was conjugated to the nanoparticle through glycosylation system (Fig. 4) [111]. The nanovaccine can significantly slow down its dissipation at the injection site and enhance lymph node drainage. This delivery vector contains B5 toxin protein module such as CTB, which can bind to GM1 receptor on the surface of APCs, thus promoting antigen endocytosis and presentation [144]. After confirming the safety, subsequent subcutaneous immunization in mice indicated that both strong antigen-specific humoral and cellular immunity were induced, providing complete protection against challenge with 5 × half-lethal dose. In addition, the safety and high efficiency of the delivery carrier were further proven in the cynomolgus monkey model [111]. Polysaccharide-conjugated vaccines are considered the most successful form of bacterial vaccines [145]. However, the traditional chemical method is a time-consuming and costly process [146], so this biological method can solve this problem by one-step fermentation and one-step purification to obtain vaccine products [147–150]. This study is also the first study to use a fully biosynthetic method to prepare a nanoscale polysaccharide-conjugated vaccine, leading to a great improvement in the immune effect.

Chitosan-based delivery systems Chitosan particles are endowed with the properties to prevent encapsulated antigen degradation and extend antigen duration time on the mucosal surface [151]. As an alternative to the oral route for chitosan particles without an additional protection from acid degradation, direct nasal immunity may stimulate the systemic and intestinal IgA immune responses. A study showed that the loading of recombinant *Shigella* MxiH antigen into chitosan nanoparticles resulted in enhanced humoral and mucosal immune responses in intranasally immunized mice [112]. In addition, various chitosan-based delivery systems are available. For example, Jahantigh et al. described a chitosan nanofibrous membrane (NF) with a high surface area to volume ratio, which is more appropriate for nasal vaccine delivery. After loading N-terminal region of IpaD (N-IpaD) antigen of *Shigella*, the guinea pigs were intranasally administered, which resulted in induction of significant serum and mucosal antibody responses and protection [113]. Moreover, O-methylated free trimethyl chitosan (TMC) nanoparticles, which have both mucoadhesive properties and excellent absorption-enhancing effects, even at neutral pH over a wide pH range for oral delivery [152], or chitosan-tripolyphosphate (CS-TPP) nanoparticles coated with Eudragit L-100 [110], were developed to further improve the immune response and protective effect of oral or intranasal routes (Table 2). However, these immune effects do not seem to be as good as those of the two previous kinds of delivery systems; thus, further optimization of chitosan or combination with other systems should be explored to enhance immune response.

Similar to the respiratory tract infections, digestive tract infections often involve bacterial colonization and invasion. Therefore, mucosal administration is also the first option for immune route, and many delivery systems such as probiotics and OMVs have shown ideal effects in protective. However, unlike the respiratory tract, mucosal delivery in the digestive tract faces more difficulties that need to be overcome, including the acidic environment in the stomach, hydrolysis by gastrointestinal proteases, immune tolerance, and intestinal microbes. In addition, the colonization of gastrointestinal pathogens does not cause easy spreading of the pathogens from person to person. Therefore, the choice of mucosal immunity or other immunization pathways should be specifically weighed. In the prevention of digestive tract infectious diseases, although there are not many studies on non-mucosal immune

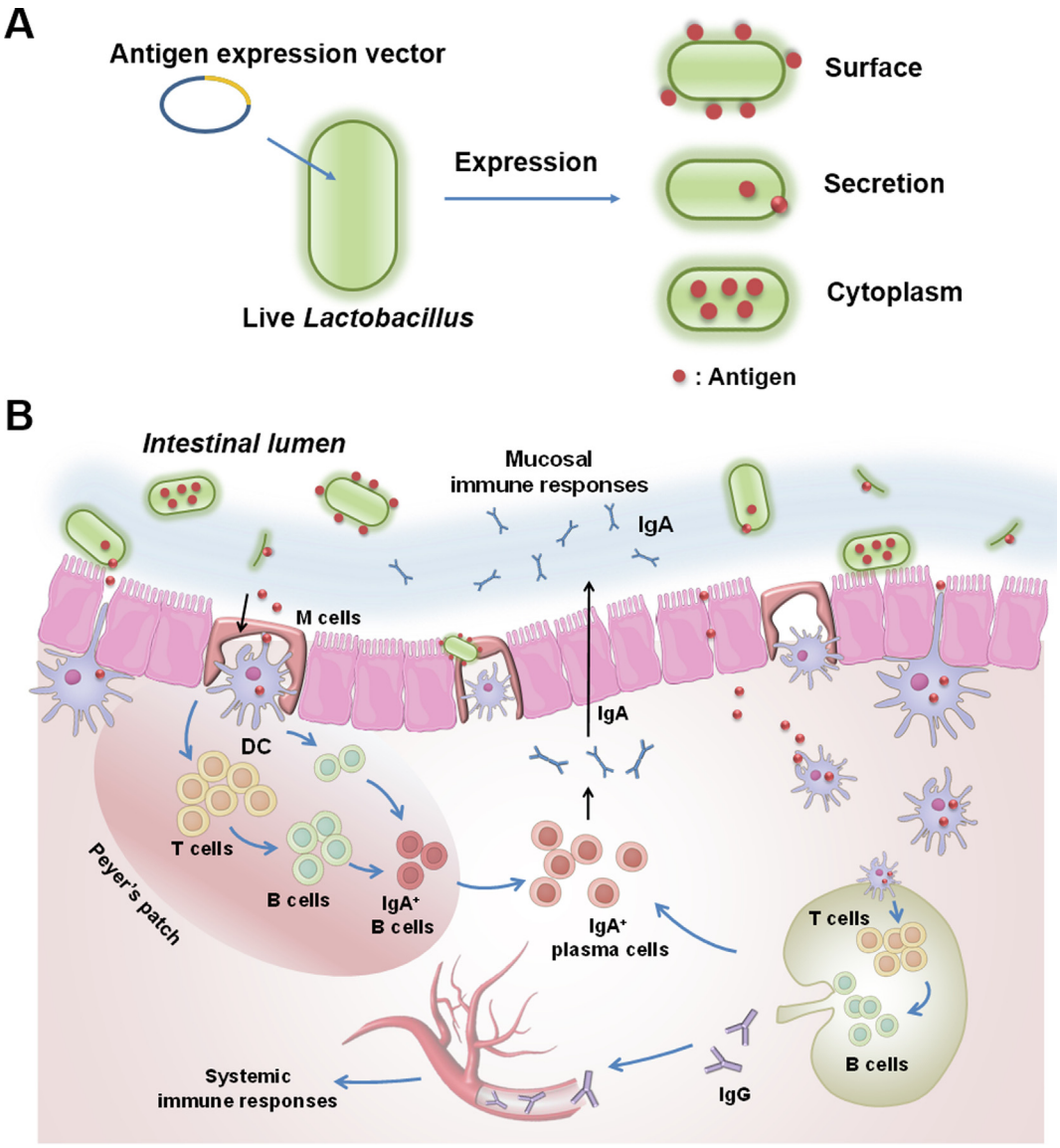

Fig. 3. Schematic diagram of construction of oral live lactic acid bacteria vector vaccine and its immune response. (A) Exogenous protein expression and localization in lactic acid bacteria. (B) Following oral vaccination, both systemic and local mucosal immune responses are induced simultaneously.

delivery systems, some have shown great potential, such as the latest bacterial B5 toxin-based protein nanocarriers.

2.3. Other pathogenic bacterial diseases and advanced delivery systems

In addition to common pathogenic bacteria that cause respiratory tract infections and diarrhea, there are many bacteria that are highly pathogenic and have various infection methods and target organs, such as *Bacillus anthracis*, *Staphylococcus aureus*, and others. In addition, some pathogenic bacteria, such as *Helicobacter pylori* and *Brucella*, cause chronic infections that are easy to relapse or difficult to cure. For the prevention of diseases caused by these pathogenic bacteria, a series of efficient delivery systems have been developed (Table 3). This section mainly focuses on the delivery systems of some important pathogenic bacteria.

2.3.1. B. anthracis

B. anthracis is the causative agent of anthrax, an acute zoonotic disease. Humans can be infected through direct contact with broken skin, contaminated meat, or inhalation [222]. The spores of *B. anthracis* have strong survival ability and are resistant to sunlight, high temperature, and disinfectants. However, the spores are easy to prepare at low cost, so they are regarded as potential biological weapons [223]. Vaccines are an effective means to prevent anthrax; however, traditional attenuated live vaccines or adsorbed vaccines have a series of problems, such as side effects, short duration of protective effect, and complicated immune procedures. For example, anthrax vaccine absorbed (AVA), the only USFDA-approved anthrax vaccine, needs to be administered six times within 18 months and enhanced once each year [224]. Therefore, the development of a safe and effective human vaccine is of great significance for the prevention and control of anthrax. So far, various delivery carriers (e.g., viral vectors, bacterial vectors, liposomes, and polymers) have been developed (Table 3). Because the main antigen of *B. anthracis* is protective antigen (PA) or its domain, it is easy to compare the effects of different delivery vehicles.

Viral vector Viral vector vaccines consist of a nonreplicating virus that contains certain genetic material from the pathogen that

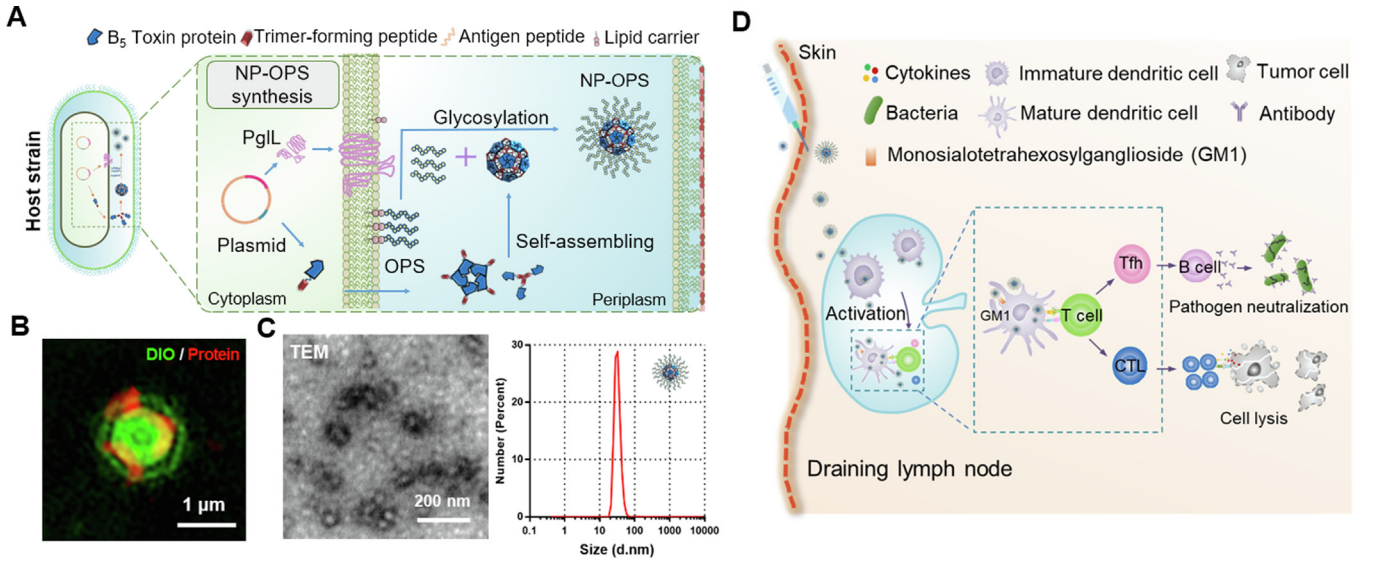

Fig. 4. Self-assembled proteinaceous nanoparticles for antigen delivery [111]. (A) Schematic diagram of protein self-assembly and conjugation with bacterial polysaccharide antigen through glycosylation system. (B) Super-resolution structured illumination microscopy images of nanoparticle-expressing bacteria. (C) Transmission electron microscopy images of the nanoparticles conjugating polysaccharide and their size distribution. (D) The vaccine can rapidly enter the draining lymph nodes and simultaneously stimulate strong humoral and cellular immune responses.

needs to be immunized. It seems to be an ideal vaccine delivery vector because of its natural viral structure, which can be well recognized by the immune system [225]. Replication-incompetent adenovirus expressing domain 4 of PA (PAD4) could induce a stronger humoral and cellular immune responses than AVA and provide full protection against lethal spore or *B. anthracis* strain challenge in a single injection in intramuscularly immunized mice [153]. Such potent protection was also reported in Semliki forest virus (SFV) vector loading PA through the challenge with the *B. anthracis* strain [154]. However, some other viral vector vaccines, such as influenza viruses and rabies virus (RV) expressing PA, were unable to induce anthrax toxin neutralization antibodies, although the antibody titers against PA were high [157,226]. Interestingly, this situation could be solved by heterologous prime/boost immunization strategy, and the particularly effective program was an initial intranasal administration of a live influenza virus vector, followed by intramuscular boosting with either the killed RV vector or the vaccinia virus vector [157]. The mechanism of this phenomenon is still unclear and one possible explanation is that the combination of different heterologous vectors may affect B-cell affinity maturation and Ig gene high frequency mutation in germinal centers. In addition, some VLP (e.g. flock house virus (FHV) VLP and bacteriophage T4 nanoparticle) vaccine were also explored; they exhibited good protection against the challenge by anthrax lethal toxin in rats or inhalational anthrax in mice, rats, and rabbits [155,156]. Although the viral vector delivery system can achieve 100% protection, some viruses such as adenovirus need to be further modified to avoid possible pre-existing immunity in humans [227].

Liposomes and polymers Other potential delivery vehicles have also been used to study anthrax vaccines. For example, PA encapsulated in liposomes containing monophosphoryl lipid A could induce full protection from lethal pulmonary challenge with *B. anthracis* spores in rabbit and monkey models [159,160]. However, liposomes are prone to oxidative degradation, resulting in low stability and short shelf life when used as delivery systems [228]. This problem can be solved with liposome-like vessels prepared by nonionic surfactant [229]. These nonionic surfactant vesicles (NISV) are self-assembling lamellar structures; they resemble liposomes because they are biodegradable, nonimmunogenic, and capable of encapsulating biologically active cargo [161,230]. Another example is a kind of chitosan nanoparticle. Liu et al. described chitosan-based microparticles (CS-NH2 MPs) with abundant amino groups. After loading PA, the formulation induced the complement system activation and enhanced antibody response [165]. Recently, Chuang et al. reported a positively or negatively charged fucoidan-quaternary chitosan nanoparticle by conjugate fucoidan (FUC) and a chitosan derivative (N-(2-hydroxy)-propyl-3-trimethyl ammonium chitosan chloride, HTCC). The surface charge was adjusted by varying the mass ratio of two polyelectrolytes. After combining FUC-HTCC nanoparticles with the approved anthrax vaccine AVA, the novel anthrax nanovaccine significantly increased the IgG antibody titers and provided complete protection compared with CpG plus AVA (75%) or AVA alone (50%) in mice exposed to anthrax lethal toxin challenge [162]. However, some other polymer particles (e.g., sucrose polymer, chitosan or its derivative, and others) need an addition of an adjuvant (e.g., CpG, mast cell activator compound 48/80 (C48/80), Poly I:C) to elicit an enhanced immune response [163,164,231]. Although mice immunized with these liposomes or polymer-based vaccines can achieve a high protection rate after challenge, the use of adjuvants reduces their competitiveness compared with viral vectors.

2.3.2. *Brucella*

Brucellosis is one of the five major zoonotic diseases in the world and seriously endangers public health. More than 500,000 new cases of brucellosis occur every year [232]. In the 21st century, brucellosis shows a rebound trend worldwide [233]. *Brucella* (the pathogen of brucellosis) is a kind of gram-negative, facultative intracellular proteus. It can be divided into more than 10 species. Among them, *B. melitensis*, *B. abortus*, and *B. suis* are the three most toxic species, which can infect both animals and humans. At present, there are no vaccines approved for human use. The animal vaccines against brucellosis are live attenuated vaccines, which still have potential serious safety risks in production and use [234].

Viral vectors Although DNA vaccines encoding *B. abortus* Cu-Zn superoxide dismutase (Cu-Zn SOD) or translation initiation factor 3 (IF3) could induce specific cellular immune response and provide protection against challenge with *B. abortus* virulent strain in mice [235,236], high concentrations and repeated doses are needed to

Table 3
Effect of vaccines with delivery systems against different bacterial challenges.

Pathogenic bacteria	Delivery system	Antigen(s)	Adjuvants used	Route	Animal species	Protection after challenge	Ref.
B. anthracis	Adenovirus	PAD4	—	i.m.	Mice	100% of animals surviving after single immunization	[153]
	SFV	PA	—	s.c.	Mice	100% of animals surviving	[154]
	FHV VLP	PA	—	s.c.	Rats	100% of animals surviving after single immunization	[155]
	Bacteriophage T4 nanoparticle	PA	—	i.m.	Mice, rats, and rabbits	100% of animals surviving	[156]
	Live influenza virus prime and killed RV vector or the vaccinia virus vector boost	PA	—	i.n. prime and i.m boost	Mice	No results	[157]
	TMV	$PA_{232-247}$ and $PA_{628-637}$	—	i.p.	Mice	Almost no protection	[158]
	Liposomes	PA	Monophosphoryl lipid A	i.m.	Rabbits and rhesus macaques	100% of animals surviving	[159,160]
	Liposome-like vessels	PAD4	Aluminium hydroxide	i.p.	Mice	70% of animals surviving	[161]
	FUC-HTCC NPs	Anthrax vaccine AVA	—	i.p.	Mice	100% of animals surviving	[162]
	Chitosan	PA	C48/80	i.n.	Mice	No results	[163]
	Chitosan derivative TMC	PA	CpG or Poly I:C or not	s.c.[a], i.m.[a], or i.p.	Mice	83.3% of animals surviving in s.c. or i.m. route	[164]
	CS-NH2 microparticles	PA	—	s.c.	Mice	No results	[165]
	Poly-l-lactide (PLLA) polylactide (PLA) microspheres	PA	—	i.m prime and either i.m. or i.n. boost	Mice	100% of animals surviving	[166]
	Dendriplex PLGA nanoparticles	PA (DNA)	—	i.m.	Mice	High antibody titer but without neutralizing activity	[167]
	PLGA nanoparticles	PAD4	—	i.p.	Mice	11% of animals surviving after single immunization	[168]
	sucrose polymer Ficoll	PA	CpG-ODN	i.m.	Mice	100% of animals surviving after single immunization	[169]
	Soybean oil-and-water nanoemulsion (NE)	PA	—	i.n.	Mice and guinea pigs	100% of animals surviving	[170]
	L. acidophilus	PA(Surface)[b]	—	No results	No	No results	[171]
	L. casei	PA[b]	—	Oral or i.n.	Mice	No results	[172]
	L. acidophilus	PA with DC-targeting peptide (Secretory)[b]	—	Oral	Mice	75% of animals surviving	[173]
	L. gasseri	PA with DC-targeting peptide (Secretory)[b]	—	Oral	Mice	100% of animals surviving and 30% of animals surviving without DC-targeting peptide	[174,175]
	S. enterica	PA, PAD1 and 4, and PAD4	—	Oral	Mice	PA: 83% of animals surviving, PAD1 and 4: 25% of animals surviving, PAD4: no protection	[176]
Neisseria meningitidis group B	*E. coli* OMV	Glycan antigens (Polysialic acid (PSA) and T antigen)	—	s.c.	Mice	50% SBA was observed at over 100-fold dilutions of the serum	[177]
Brucella	SFV	Cu-Zn SOD	—	i.p.	Mice	1.52 (3.07–1.55)[c]	[178]
		IF3	—	i.p.	Mice	1.09 (6.96–5.87)[c]	[179]
	Influenza virus	L7/L12 or Omp16	—	i.n., eyedrop[a], or s.c.	Mice	The best: Omp: 16: 3.78 (4.54–0.76)[c], eyedrop; Bivalent: 3.9 (4.54–0.64)[c], eyedrop	[180]
	Influenza virus	Tetravalent vaccine formulation expressing Omp16, L7/L12, Omp19, and Cu-Zn SOD	—	i.n.[a], eyedrop, or s.l.	Guinea pigs	The best: 2.8 (2.86–0.06)[c], i.n.	[181]
	L. lactis	L7/L12 (Cytoplasm)[b]	—	Oral	Mice	0.57 (7–6.43)[c]	[182]
		Cu-Zn SOD (secretory)[b]	—	Oral	Mice	1.35 (7.1–5.75)[c]	[183]
	L. lactis (Live or killed)	Omp31 (Cell Wall-Anchored)[b]	—	Oral or i.p.	Mice	No results	[184]
	Attenuated *S. typhimurium*	Fusion of L7/L12 and BLS[b]	—	Oral	Mice	Secretory expression: 1.55 (4.44–2.89)[c]; Intracellular expression: 1.32 (4.44–3.12)[c]	[185]
		L7/L12	—	i.m.	Mice	About 1.7 (3.4–1.7)[c]	[186]
	Ochrobactrum anthropi	Cu-Zn SOD	CpG	i.p.	Mice	2.42 (5.30–2.88)[c]	[187]
	TMC	Omp19	—	Oral[a] or i.p.	Mice	The best: against *B. abortus*: 2.46 (6.3–3.84)[c], oral; against *B. melitensis*: 2.38 (6.14–3.76)[c], oral	[188]

Table 3 (*continued*)

Pathogenic bacteria	Delivery system	Antigen(s)	Adjuvants used	Route	Animal species	Protection after challenge	Ref.
	Mannosylated chitosan nanoparticles	FliC	—	s.c.	Mice	Against *B. melitensis*: 1.34 (5.67–4.33)[c]; against *B. abortus*: 1.22 (5.24–4.02)[c]	[189]
	escheriosome	L7/L12	—	s.c.	Mice	1.46 (4.58–2.93)[c]	[190]
		Cu-Zn SOD	IL-18	s.c.	Mice	1.5 (5.2–3.7)[c]	[191]
	PLGA	L7/L12	—	i.p.	Mice	1.79 (5.94–4.15)[c]	[192]
	CaPNs	FliC, 7α-HSDH, BhuA and multi-epitopes (Poly B and poly T)	—	s.c.	Mice	The best: against *B. melitensis*: Poly B + T, 1.5 (5.77–4.27)[c]; against B. abortus: Poly B + T, 1.37 (5.29–3.92)[c]	[193]
S. aureus	OMV (*E. coli*)	Hla_{H35L}, SpA_{KKAA}, FhuD2, Csa1A, and LukE	Alum	i.p.	Mice	90% of animals surviving	[194]
	PDNVs (*E. coli*)	SAcoagulase	—	i.p.	Mice	100% of animals surviving	[195]
	extracellular vesicles (EVs)	Hla_{H35L}, LukE and EVs components	—	s.c.	Mice	About 70% and 50% of animals surviving after challenging with two *S. aureus* isolates	[196]
	ICG-loaded MSNs	EVs	—	s.c.	Mice	Decreased bacterial loading in skin and organs	[197]
	PDNVs	PDNVs components	—	s.c.	Mice	No results	[198]
	L. lactis	ClfA[b] and FnbpA[b]	Freund's adjuvant	Unknown	Rats	Less infected vegetations after challenging with *S. aureus* Newman in *L. lactis* ClfA-immunized animals; FnbpA did not have the same effect	[199]
	PilVax	B-cell epitope, D3, from FnbpA	—	i.n.	Mice	Decreased bacterial loading in intestine and nasal mucosa	[200]
	Cowpea mosaic virus	D2 domain of FnbpB	—	i.n. or oral	Mice	No results	[201]
	Live attenuated *S. typhimurium*	SaEsxA[b] and SaEsxB[b]	—	Oral	Mice	22.2% and 44.4% of animals surviving after challenging with *S. aureus* USA 300 for SaEsxA and SaEsxB; no animals surviving after challenging with *S. aureus* Newman	[202]
	Red blood cell membrane-coated PLGA	Hla, α-toxin, PVL, and γ-toxin	—	s.c.	Mice	Decreased bacterial loading in skin, blood, and organs	[203,204]
	PP7 (VLP)	AIP1S	—	i.m.	Mice	Inhibiting abscess area and dermonecrotic; Decreased bacterial loading at the site of infection	[205]
	PLGA	CNA19	—	s.c. or i.n.	Mice	No results	[206,207]
	PLGA	rSEA	—	i.p.	Mice	100% of animals surviving	[208]
	Chitosan	rSEB	—	i.n.		No results	[209]
	Chitosan	Ami		No results	No results	No results	[210]
	Liposome	AdsA (mRNA)	—	i.m. or s.c.	Mice	No results	[211]
H. pylori	*L. lactis* (GEM)	CUE	—	Oral	Mice	Decreased bacterial loading in gastric tissue	[212,213]
	L. acidophilus	Hp0410	—	Oral	Mice	Decreased bacterial loading in gastric tissue	[214]
	L. plantarum	Urease Bsubunit (UreB) (Cytoplasm)[b]	—	Oral	Mice	Decreased bacterial loading in gastric tissue	[215]
	HP55/PLGA nanoparticles	Recombinant antigen CCF	—	Oral	Mice	Decreased bacterial loading in gastric tissue	[216]
	OMVs	OMV components	—	Oral	Mice	Decreased bacterial loading in gastric tissue	[217]
	liposomes	Fusion of the urease linear epitope (19 amino acid residues) and CTB	—	Oral	Mice	Decreased bacterial loading in gastric tissue	[218]
Yersinia pestis	Bacteriophage T4 nanoparticles	Mutated capsular antigen F1 and low-calcium-response V antigen	—	i.m.	Rats	100% of animals surviving	[155]
	20:80 CPTEG:CPH	Fusion of F1 and V antigens	Cyclic dinucleotides (CDNs)	s.c.	Mice	100% of animals surviving at 14 days and 75% at 182 days after single immunization	[219]
	OMVs	OMV components	—	i.m.	Mice	100% of animals surviving in subcutaneous challenge; 100% and 50% of animals surviving in intranasal challenge with a median and a high dose	[220]
	L. plantarum	LcrV (Surface)[b]	—	Oral	Mice	No results	[221]

a. The better or the best route to achieve protection; b. Constructed in an expression vector; c. Log_{10} units of protection, obtained by subtracting the mean log_{10}CFU for the experimental group from the mean log_{10} CFU for the corresponding control group; i.n., intranasal; s.c., subcutaneous; i.m., intramuscular; i.p., intraperitoneal; s.l., sublingual; —, without added adjuvant.

improve *in vivo* transfection efficiency. So far, some viral vectors (SFV vectors, and especially influenza viral vectors) have been developed, with high safety and immunogenicity demonstrated in various models (chicken, ferrets, rhesus macaques, and humans) [178,179,237–239]. Influenza viral vectors may be a promising candidate for human use because of the lack of pre-existing immunity in humans. After immunization with recombinant influenza A viruses of the subtypes H5N1 and H1N1 expressing *Brucella* protective antigen (ribosomal protein L7/L12 or Omp16), a strong cellular immune response and protective effect were induced, even comparable with those induced by a commercial *B. abortus* S19 vaccine [180]. Further, a tetravalent vaccine formulation (expressing Omp16, L7/L12, Omp19, and Cu-Zn SOD in recombinant influenza viral vector subtype H5N1 without an adjuvant) was developed to prevent human brucellosis [181,240]. In addition, because *Brucella* can infect people of any age, the long-term protection of this viral vector vaccine also needs to be considered.

Bacterial vectors *L. lactis* can be used as a delivery system by expressing *B. abortus* antigen in the cytoplasm, cell wall, or extracellularly [241]. However, the final protective effect may be related to the antigen type and its location. For example, oral administration of *L. lactis* expressing L7/L12 in the cytoplasm only provided partial protection in mice [182], while secretory expression of Cu-Zn SOD induced protective immunity similar to positive controls (immunized with *B. abortus* strain RB51) [183]. Studies on attenuated *S. typhimurium* vector indicated that secretory expressing *Brucella* L7/L12 or fusion antigen (fusing L7/L12 and lumazine synthase (BLS)) could induce stronger humoral and cellular immune responses and higher protection against *Brucella* infection than intracellular expressing vectors [185,186]. Thus, construction of *L. lactic*-based vaccines with secretory expressing *Brucella* antigens may be a more suitable way to induce protective immunization. Because *Brucella* is an intracellular bacterium, cellular immunity is relatively more important and this response could be strengthened through the addition of CpG adjuvants [187]. It was found that mucosal immunization could also provide protection from mucosal infection by *B. abortus* [185]. Therefore, the choice of appropriate adjuvants and mucosal route are beneficial for inducing the protective response against *B. abortus* infection.

In addition, some other delivery systems, such as chitosan derivatives (TMC and mannosylated chitosan nanoparticles), liposomes, polymers, and inorganics were used for vaccine design [188–193]. Although there have been few reports about these delivery vehicles, some of them have shown promising application prospects.

2.3.3. S. aureus

S. aureus is a pathogenic bacterium that causes a wide spectrum of human infections, inducing severe skin lesions, pneumonia, bacteremia, and meningitis. Overuse of antibiotic regimens has led to the emergence of resistance, which presents a great challenge to clinical treatment.

OMVs have been widely explored for the development of vaccine against *S. aureus*. For example, OMVs from modified *E. coli* were decorated with five *S. aureus* protective antigens by fusion expression with lipoprotein leader sequence. The concentration of antigens reached 5%–20% of total OMV proteins, and great protection was demonstrated in three mouse infection models (a sepsis model, a renal abscess model, and a skin infection model) [194]. Generally, although the removal of LPS reduced the toxicity of OMVs, there are still many toxic proteins on the outer membrane [242]. Kim et al. designed bacterial protoplast-derived nanovesicles (PDNVs) by depleting toxic outer membrane components of *E. coli* to improve the security and productivity of OMVs. This delivery platform could load different antigens. In immunized mice, strong antigen-specific humoral and cellular immune responses were induced, and full protection from lethal challenge with *S. aureus* was observed [195]. In addition, the OMVs of *S. aureus* itself were also used to prepare vaccines because they contain a variety of antigen components. Wang et al. prepared engineered extracellular vesicles (EVs) by expressing non-toxic Hla_{H35L} and LukE in a *S. aureus* mutant strain. The animal experiment results indicated that the engineered EVs could induce stronger specific antibody response and protect mice in a lethal sepsis model. Further, an array of bacterial antigens, such as lipoproteins, exotoxins, and cytoplasmic proteins, could also be encapsulated as a vaccine platform [196]. Since *S. aureus* can invade and survive inside host cells, cellular immunity is also needed. By coating EVs on the surface of indocyanine green (ICG)-loaded magnetic mesoporous silica nanoparticles (MSNs), endocytosis EVs can escape from lysosomes through their breaking by heating ICG with laser irradiation, and improved $CD8^+$ T cell responses were induced to prevent and treat *S. aureus* infection [197].

Generally speaking, there are two main strategies to prepare *S. aureus* vaccines using microbial secreted vesicles. One is to express *S. aureus* antigen in *E. coli* and the other is to load the antigen in secreted OMVs. As an engineering strain, *E. coli* is more convenient for gene operation, and it can be easily optimized. For the other, the EVs of *S. aureus* itself contain a large number of antigen components, so they may also be a potential candidate. However, the main problem to be solved includes the safety of EVs because EVs contain biologically active toxins and induce a strong inflammatory response [243–245].

For some pathogenic bacteria with various infection forms and target organs, a variety of advanced delivery systems have been developed; among them, biological vectors such as viral vectors and probiotic vectors have been widely used. For a *B. anthracis* vaccine, the antigen is relatively unique, so different delivery systems are more comparable. It has been found that the immune effect of viral vectors from animal experiments is better than that of probiotic vectors, which was also revealed in the *Brucella* vaccines studies. For this phenomenon, in addition to the carrier itself, the immunization method and immunization dose may also be important factors. Furthermore, due to the variety of bacteria, the same delivery system in different pathogenic bacteria vaccine research will provide references for the general application of an advanced delivery system.

3. Viral infection diseases and advanced delivery systems

Among infectious diseases, viral infections are one of the leading causes of mortality worldwide. They usually evolve to cause a global life threat and socioeconomic recession. Despite the huge challenges of the ongoing COVID-19 pandemic, the achieved progress on the drug treatment of other viruses (e.g., Ebola viruses, *human immunodeficiency virus* (HIV), and hepatitis viruses) is impressive. To overcome this hurdle, advanced vaccine delivery systems are more urgently required.

3.1. Major epidemic viral infections and prevention challenges

According to International Committee on Taxonomy of Viruses (ICTV), there are 36 classes, 168 families, and 6590 species of viruses (Virus Taxonomy: 2019 Release) [246]. Among the infectious viruses, an overwhelming majority of the viral infections lack the specific drugs, and vaccines have historically been the foremost effective means to save people's lives. Recent epidemic virus diseases and major vaccine products or clinical candidates are listed in Table 4.

3.1.1. Hepatitis B virus (HBV)

Globally, more than 290 million people are living with HBV [261]. HBV attacks the liver and accounts for more than 900,000 deaths per year. Under the worst-case scenario, there will be a projected 5.3 million additional chronic HBV infections among children born between 2020 and 2030 and one million additional HBV-related deaths among those children. The next-generation HBV vaccination is expected not only to prevent the virus infection, but also to accelerate the elimination of viral hepatitis or even cancer.

3.1.2. Influenza virus

During the 1918 influenza pandemic, 20–40 million deaths occurred in the second phase of the outbreak. Antigenic shifts and mutations of the genome between different species of influenza result in the high degree of variation, thereby enabling the emergence of novel influenza strains and drug resistance [262]. Every year, the WHO predicts the possible prevalent virus types and suggests the components for producing the influenza vaccines. However, the emergence of new strains continues to pose a public health threat. Therefore, an advanced vaccine delivery system with cross-protection efficacy would be very desirable.

3.1.3. Human papillomavirus (HPV)

HPV is the most common sexually transmitted infection, with the lifetime probability of acquiring HPV ranging between 85% for women and 91% for men. HPV vaccination is an effective primary prevention strategy to reduce HPV infections that can lead to cancer (e.g. cervical, vaginal, anal, and penile cancer) [263]. Although clinical trials of Gardasil and Cervarix have been extremely promising, these first-generation vaccines are not ideal vaccine candidates. Researchers are actively working on the development of other HPV vaccines or delivery systems that may be more effective against a broader range of HPV types (e.g., Gardasil 9-valent vaccine), cheaper (e.g., Cecolin), easier, or even therapeutic.

3.1.4. Ebola virus

Ebolavirus is a highly lethal viral pathogen that belongs to Filoviridae (filament-like viruses). It causes viral hemorrhagic fever. The 2014–2016 Ebola epidemic resulted in more than 28,000 cases and more than 11,000 deaths. Ervebo is the first vaccine licensed by FDA in 2019 for the prevention of Ebola virus disease [250], and over 218,000 doses have been administered to individuals, as of 2020. The vaccine is a recombinant live-attenuated *Vesicular stomatitis virus* (rVSV) in which the VSV-G envelope glycoprotein (GP) has been completely replaced by the Zaire ebolavirus GP (rVSVΔG-ZEBOV-GP). The data on immunogenicity demonstrate that anti-GP antibodies are generally detectable by 14 days after vaccination, with up to 100% seroconversion observed by 28 days after the dose [264]. Nevertheless, vaccine candidates with relatively short time to immunity after antigen challenge are still under development for immediate public health responses.

3.1.5. SARS-CoV-2

The novel coronavirus SARS-CoV-2 causes coronavirus disease 2019 (COVID-19), which was declared a pandemic on March 11, 2020 by the WHO. Presently, COVID-19 affects most countries on our planet with the result of 163,869,893 confirmed cases, including 3,398,302 deaths, as of May 19, 2021 (https://covid19.who.int/). The pandemic has been considered the worst crisis since the World War II. Vital organs including the heart, liver, kidneys, gastrointestinal tract, and the central nervous system can be affected, causing multiple organ complications [7]. Fortunately, under global efforts, 15 COVID-19 vaccines have been developed at an unprecedented speed (as of May 7, 2021, the main examples can be seen in Table 4). The protection rates (>90%) of the first COVID-19 vaccines are exciting [265], and a reduction rate of 85% in BNT162b2 vaccine recipients has been newly reported [266].

3.1.6. HIV

The emergence of AIDS was first reported in 1981, followed by the identification of HIV as the cause of the disease. HIV/AIDS is now a global pandemic, and 32.7 million people have died from AIDS-related illnesses (as of 2019, according to the Global HIV & AIDS statistics-2020 fact sheet). Recently, an RV144 vaccine that contains canarypox vector ALVAC-HIV (vCP1521) prime and AIDSVAX®gp120 B/E protein boost advanced to phase III clinical trials in Thailand, which shed light on the recent progress. The protection rate was reported to be 31.2% [257]. However, several vaccine candidates (e.g., Env DNA-rAd5) failed to induce the antibodies with

Table 4
The major virus-related diseases and vaccine development.

Virus	Remarkable vaccines	Developer	Adjuvants used	Approval / Clinical	Vaccine type/Reference
HBV	Recombivax HB	Maurice Hilleman	Alum	1986	Subunit [247]
Influenza Virus	Inflexal® V	Crucell Berna Biotech	Virosomal	1997	Inactivated [248]
HPV	Gardasil®/Gardasil® 9	Merck	Alum	2006/ 2014	Recombinant [249]
	Cervarix®Cecolin	Glaxo Smith KlineInnovax	AS04Alum	20072019	Recombinant [249] Recombinant
Ebola	Ervebo®VSV-EBOV-GP	Merck	—	2019	Attenuated [250 251]
SARS-CoV-2	mRNA-1273	Moderna	Liposome	2020	mRNA vaccine [252]
	AZD1222	University Oxford/Astra Zeneca	—	2020	Adenovirus vector [253]
	Tozinameran(BNT162b2)	Pfizer & BioNTech	Liposome	2020	mRNA vaccine [254]
	BBIBP-CorV	Beijing Institute of Biological Products	Alum	2021	Inactivated [255]
	Ad5-nCoV	Beijing Institute of Biotechnology	—	2021	Adenovirus vector [256]
HIV	ALVAC-HIV (vCP1521) prime, ALVAC-HIV /AIDSVAX gp120 boost	Thai Component and U. S. Army Medical Component	—	Phase II	RV306/NCT01931358 [257]
Noroviruses	GI.1/GII.4 Bivalent Virus like particle (VLP) Vaccine	TAKEDA benchmark	Alum	Phase II	NCT02153112 (Child); NCT02475278 (Adult) [258]
	Norwalk VLP Vaccine	LigoCyte Pharmaceuticals	Chitosan/ MPL	Phase II	NCT00806962 [259]
MERS	MVA-MERS-Sin escalating dose regimes	Marylyn Addo	—	Phase I	Attenuated [260] NCT03615911

neutralization activity [267], and the first licensed vaccine is long expected.

3.1.7. Norovirus

Noroviruses are a major cause of acute gastroenteritis (AGE) around the world. They are transmitted through the fecal–oral route. This virus leads to 200,000 children deaths every year. Recently, the vaccine candidates have focused on the Norovirus VLP Vaccines. One of the most promising candidates is GI.1/GII.4 Bivalent VLP Vaccine with alum adjuvant in phase 2, from Takeda benchmark [258]. This formulation elicits robust immune responses, as Pan-IgG (>93%), IgA (>93%), and antigen-blocking antibodies (>83%) are already evident 8 days after vaccination. The other candidate is the intranasal Norwalk VLP Vaccine with chitosan/MPL adjuvants in phase 2 from Ligocytes [259]. IgG and IgA antibodies increased 4.8- and 9.1-fold, respectively, for the 100-μg dosage level. Although AGE is partially self-limited, it is also associated with a higher risk of severe or fatal consequences in vulnerable age and in the older persons with chronic diseases. In the near future, the development of norovirus vaccine should be expedited.

3.2. Delivery strategies against virus infection

Despite the broad medical impact from the vaccination, there are numerous globally devastating virus diseases without fully protective vaccines. As shown in Table 4, HIV vaccines are still restricted to the clinical trial phase. Even if the tested vaccine candidates help to produce antibodies, the protection (31.2%) may be inadequate. The poor efficacy is highly due to the lack of an efficient adjuvant/delivery system rather than the poor specificity of antigens. In this context, it is more important to develop a vaccine delivery system with high efficiency, long-term efficacy, or cross-protection. Efforts also include the material-based nano/microparticles, biological exosomes, or integrated vehicles, which are described in the section about prophylactic vaccines against bacterial diseases (2.1–2.3). In this section, we further highlighted the advanced vaccine delivery strategies that can meet the fundamental requirements for controlling the virus infections.

3.2.1. Advanced delivery strategy for robust/high protection efficiency

For the sudden outbreaks of virus infection (e.g., COVID-19 and Ebola), there is an urgent need to provide robust/high preventive vaccination. Although a few vaccines were licensed in emergency, these first-generation vaccines still need to achieve a higher protective efficacy in a timely manner to end the pandemic. To obtain a similar rapid protection but a much better safety, advanced micro/nano delivery systems with safer antigens (subunit or peptide antigens) are being explored. These vaccine delivery platforms involve synthetic particles, proteinaceous particles, rebuilt particulate adjuvant, and an integrated device.

i) Synthetic or proteinaceous micro/nano particles offer great utility in robust vaccine design. Ma's group has designed a series of micro/nanoparticle as "Chassis" to mimic natural pathogen (shape, fluidity, or other properties), and assembled antigen and other components (e.g., adjuvant) on/in it to obtain a synthetic vaccine [8,268]. For example, the polylactic-co-glycolic acid (PLGA) nanoparticles-stabilized Pickering emulsion (the core was liquid oil and the antigen was loaded in the nanoparticle gap among the oil surface) showed virus-mimicking deformability/mobility. In virtue of these advantages, the highest protection percentage of H1N1 vaccine was obtained with this chassis. The safety and efficacy were far better than those with commercial adjuvants (e.g., MF59). In another example, researchers developed a nanoparticle vaccine by covalently conjugating the self-assembled 24-mer ferritin (Ft) with the receptor binding domain (RBD) and/or heptad repeat (HR) subunits of SARS-CoV-2 S protein. The nanoparticle vaccination of rhesus macaques induced significantly higher neutralizing antibodies and T and B cell responses prior to boost immunization [269]. Since the components of Ft nanoparticles are from nature, this proteinaceous delivery system is of higher safety than the vaccines harboring artificial materials. However, the virus-mimicking system via the synthetic chassis (prepared of an FDA-approved material) also has translation merits, which facilitates the widespread vaccinations to curb the virus.

ii) Incorporating traditional vaccines adjuvants with advantageous physicochemical properties (e.g., size and mobility) is an intelligent manner to develop safe and efficient vaccines within a short time frame. As the most accessible adjuvant, alum is still the sole employed adjuvant in most countries. However, it tends to attach on the membrane rather than to enter the DCs, leading to the absence of intracellular process of the antigens, and thus limits T cell-mediated immunity. Xia et al. packed alum on the squalene/water interphase, forming an alum-stabilized Pickering emulsion (PAPE) [270]. "Inheriting" from alum and squalene, PAPE demonstrated a good biosafety profile. With the dense array of alum on the oil/water interphase, PAPE not only adsorbed large quantities of SARS-CoV-2 antigens, but it also harbored a higher affinity for DC uptake, which provoked the uptake and cross-presentation of the delivered antigens. Compared with alum-treated groups, more than six times higher antigen-specific antibody and three-fold more IFN-γ-secreting T cells were induced, indicating the potent humoral and cellular immune activations (Fig. 5). This work provided important insights towards a safe and efficient adjuvant platform for enhanced COVID-19 vaccines.

iii) Novel administration route with integrated nanoparticles vaccines helped to catalyze vaccine candidates at a greater speed. Yang et al. described a method of Ebola vaccine using a DNA antigen coated on PLGA-polyl-lysine/poly-γ-glutamic acid (PLGA-PLL/γPGA) nanoparticle via a microneedle (MN) patch [271]. IgG1 subtype responses were significantly higher after immunization with nanoparticle (intramuscular injection) and still higher when administered by MN patch, while the MN patch showed the highest neutralizing activity, neutralizing over 50% of GP-pseudovirions. Chen et al. reported an influenza vaccination via sustained intradermal (ID) release of vaccines using implantable and patch-free chitosan MN. Chitosan MNs can be quickly and entirely implanted into the dermis to function as a depot and an immune-boosting agent for the extended release of vaccines and simultaneous activation of the immune system. The MN-induced immune-enhancing effect lasted for at least 16 weeks [272]. These integrated delivery systems enable precise vaccine administration by minimally trained personnel and even enhance the vaccine potency. In addition, the MN provides vaccine stability without refrigeration; it is expected to be manufactured at low cost to meet the needs of developing countries.

3.2.2. Advanced delivery strategy for long-term protection

Persistent protection is required against the virus with long incubation periods (e.g., 5–10 years for HIV infection) or resultant chronic diseases/cancer (e.g., HBV-induced liver cancer). These diseases even pose fatal challenge for the infectors that have access to anti-virus drugs. In this case, a vaccine with long-term prophylactic efficacy or a therapeutic effect was appreciated. Therefore, vaccine delivery strategies for protecting the antigen (protein or RNA) payload from environmental enzyme degradation or inducing cytotoxic T-cell activity against the infected cells are highly appreciated.

i) Advanced delivery systems (e.g., micro/nano formulation, hydrogel) are an important strategy for sustained antigen release. Protein/peptide/drugs are easily degraded by hydrolysis and enzymes in the human body, which results in their short half-life

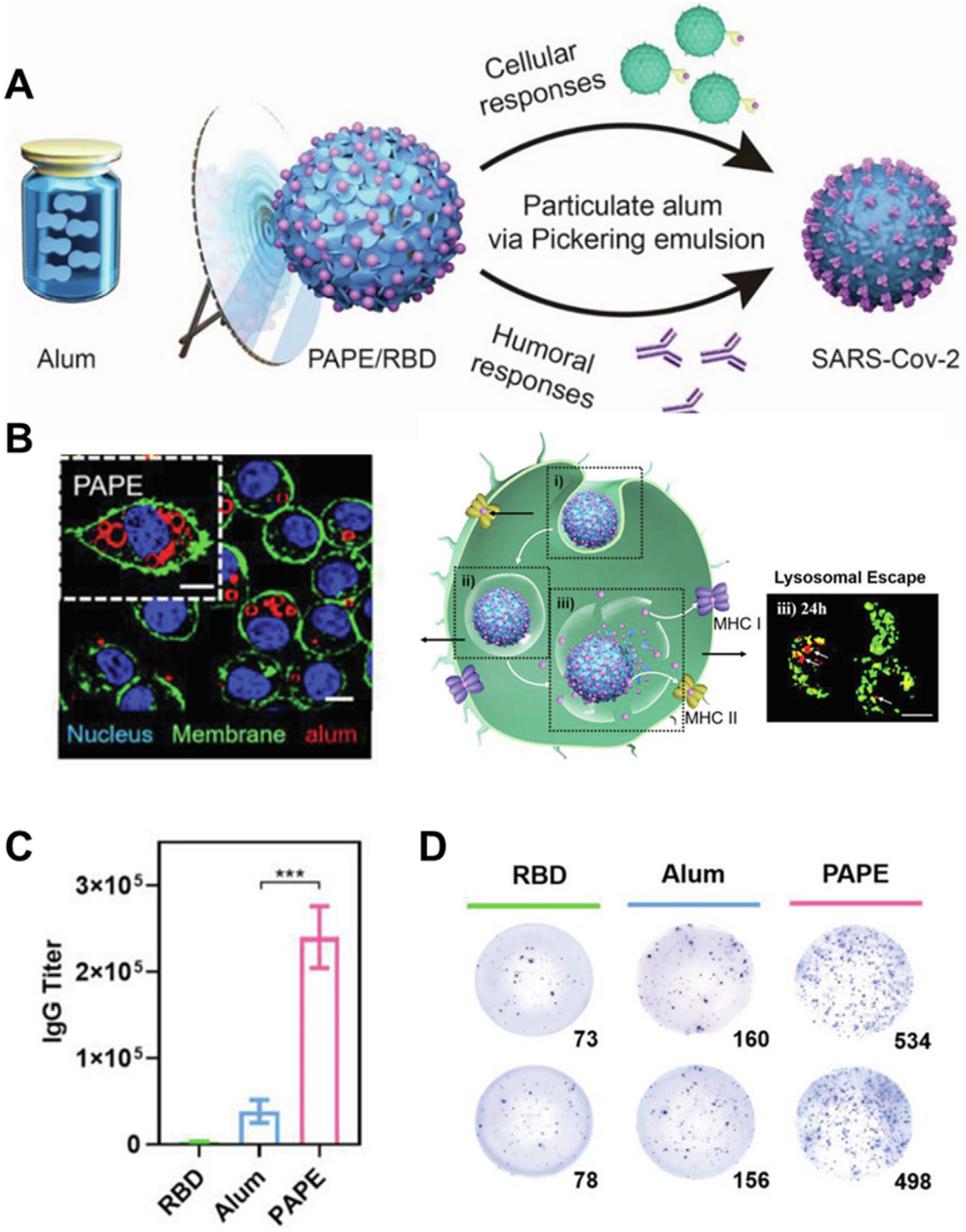

Fig. 5. Particulate alum via Pickering emulsion as an enhanced COVID-19 vaccine adjuvant. (A) Schematic illustration of PAPE strategy. By "mirroring" clinically approved alum, PAPE "inherited" its acknowledged biosafety profile. (B) Efficient uptake of PAPE (red color in the left confocal images) and lysosomal escape (as indicated by the white arrow in the right penal) were acquired for the PAPE group. Scale bar = 10 μm. (C-D) Potent humoral and cellular response to SARS-CoV-2 RBD vaccinations. (C) Serum RBD-specific IgG titer. (D) ELISpot analysis of IFN-γ-spot-forming cells among splenocytes. Reprinted from [270], Copyright 2020, with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

time and the need for frequent injections. Once loaded on micro/-nano materials, physical protection or controllable release could be obtained with the material degradation for persistent outcome.

Lipids or polymers with good biocompatibility or degradability are attracting a great deal of interest among vaccine delivery systems. The success of the COVID-19 RNA vaccines from either Pfizer or Moderna is highly dependent on the novel lipid delivery system. These lipid nanoparticles substantially improved the stability of the mRNA and facilitated the RNA transfection efficiency *in vivo* [6]. Tian et al. fabricated a nanovector composed of peptide-based nanofibrous hydrogel, which was able to condense DNA and result in strong immune responses against HIV [273]. This nanovector was able to strongly activate both humoral and cellular immune responses in a balanced way, a result rarely reported in previous studies, which is crucial for HIV prevention and therapy. The nanofibrous structure of the hydrogel is critical for the dramatically improved immune responses compared with the existing materials.

A delivery system with the optimum size, structure, and properties could facilitate a long-acting antigen-specific response. Xi et al. reported a poly(lactide-co-glycolide) PLGA microcapsule-based formulation for high-performance vaccinations (Fig. 6) [274]. The special self-healing feature provides a mild and efficient paradigm for antigen microencapsulation. Although without traditional molecular adjuvant, these microcapsules could still create in situ beneficial immunization microenvironments at the vaccination site, wherein sustained antigen release, constant APC recruitment, and favorable acidic surrounding collaborated effectively. As

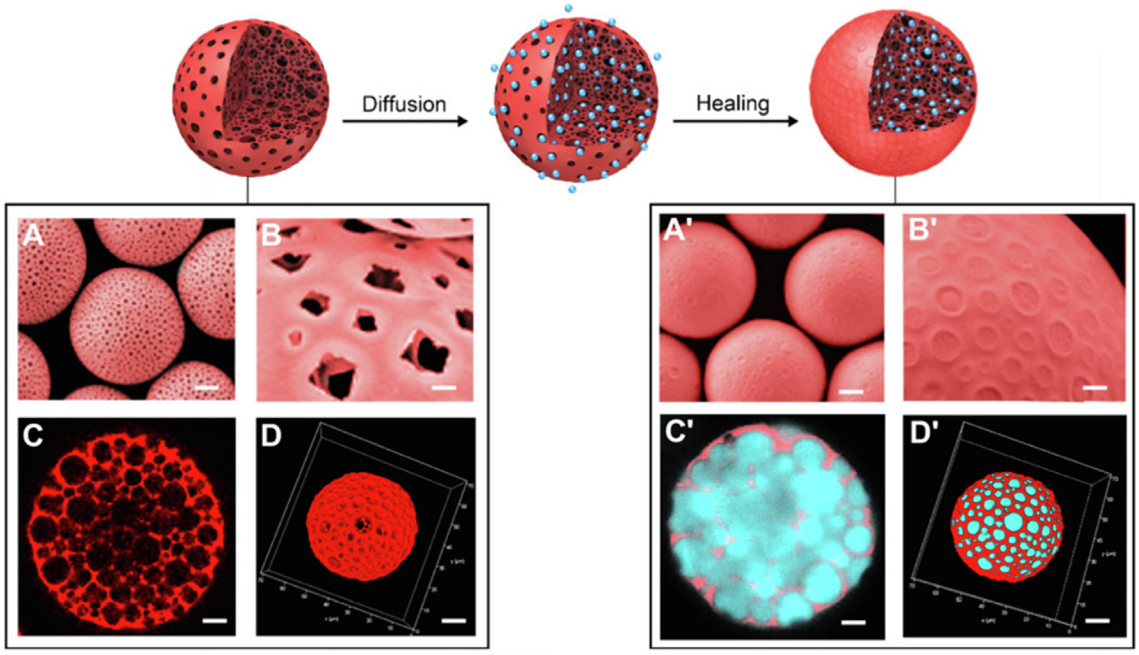

Fig. 6. Strategy of using self-healing microcapsules to modulate immunization microenvironments for vaccination [274]**.** The corresponding characterizations of gigaporous microspheres and antigen-loaded microcapsules are displayed below: (A and A′) Scanning electron microscopy (SEM) images in a magnified view. Scale bars, 10 μm. (B and B′) SEM images in a local feature. Scale bars, 1 μm. (C and C′) Confocal images in two-dimensional (2D) cut view. Scale bars, 5 μm. (D and D′) 3D reconstruction. Scale bars, 10 μm.

a result, effective T cell response and prevention of postsurgical recurrence were acquired with various types of antigens. Wu et al. developed a thermal-sensitive hydrogel (a formulation of chitosan derivate and glycerophosphate) as intranasal H5N1 vaccine delivery system [275]. In terms of the thermal sensitivity and intensive positive charge, this hydrogel efficiently extended the residence time of antigen in the nasal cavity and promoted the central/effector T_{RM}. Although a wave of efforts have spurred to improve the vaccine effect, these delivery systems were endowed with controllable attributes along with a persistent performance, which is promising to encapsulate other virus antigens and avoid frequent vaccination.

ii) The enhanced antigen-specific cytotoxic T-cell (CTL) response is considered a promising strategy to prolong the vaccine efficacy. The sustained efficacy is possibly due to the repetitive antigenic surfaces that mimic influenza pathogenic structures, which activate the host immune system to fight against and finally cause the lysis of the pathogens. For example, Wang et al. fabricated double-layered protein nanoparticles via ethanol desolvation and chemical cross-linking of influenza matrix protein 2 ectodomain-neuraminidase (M2e-NA) recombinant proteins [276]. The layered M2e-NA nanoparticles induced a strong CTL response, contributing to long-lasting immune protection. In addition, extracellular vesicles (exosomes) released from $CD8^+$ T cells contained antiviral membrane-bound factors that inhibited HIV-1 transcription in both acute and chronic infection models [277].

To achieve efficient CTL response, Ma's group has developed various particulate strategies for enhanced cross-presentation [8], including positive charge, gas generating, ligand modification, and membrane fusion. For example, inspired by an important natural biological behavior, membrane fusion, Hu et al. constructed a pH-responsive nanocarrier (HBsAg&CpG@Lip) with a membrane fusion capacity for HBsAg intracellular delivery and subsequent processing by T cells (Fig. 7). This nanoparticle not only elicited a higher anti-HBsAg IgG and IgG2c/IgG1 ratio, but it also augmented the strong CTL response [278]. Lu et al. integrated a physiochemical merit (positive charge) and an immunopotentiator property (stimulator of interferon genes (STING)) in poly (lactic acid) (PLA) microparticles. Such a microparticle-based vaccine achieved 50% HBsAg seroconversion rate, reduced HBcAg in the liver, and also produced higher amount of memory T/B cells to confer protection in a sustained manner [279]. Although a much longer protection efficacy was not monitored, these studies opened alternative avenues for potent therapeutic vaccines, which is particularly important for the chronic infectors without efficient drugs.

3.2.3. Advanced delivery strategy for cross-protection

Viruses are able to adapt to the changing environment, demanding a cross-protection immune response for the evolved multiple strains. Such a merit is particularly important when the virus mutates annually (e.g., Influenza virus) or raises the risk of coinfection with other pathogens (e.g., HPV). For example, antibodies produced from most influenza vaccines are strain-specific and display poor cross-reactivity with virus hemagglutinins of alternative subtypes [280]. In addition, cross-neutralizing titers, when noted, tend to be at least 100 times lower than type-specific titers and, therefore, cross-protection might be less durable than type-specific protection [281]. Recently, the strategy for cross-protection has mainly focused on incorporating a high conservative virus subdomain or eliciting the $CD8^+$ T cell immunity or T-follicular helper (Tfh) cell immunity.

i) Utilizing the conservative virus subdomain is promising for achieving the cross-protection efficacy. Since HR is highly conservative in the coronaviruses evolution and harbors cross-reactive SARS-CoV-2 T-cell epitopes, the HR subdomain within S2 region of S protein is noticed. HR-containing nanoparticle vaccines were demonstrated to produce neutralizing antibodies against SARS-CoV, MERS-CoV, HCoV-229E, HCoVOC43, and RATG13 [269]. In addition, they induced higher percentages of Tfh and B cells within germinal centers, as well as IgG1 and IgG2b memory B cells. As B cell maturation relies on the coordination with Tfh, it is possible that $CD4^+$ T epitopes within HR facilitate Tfh to recognize

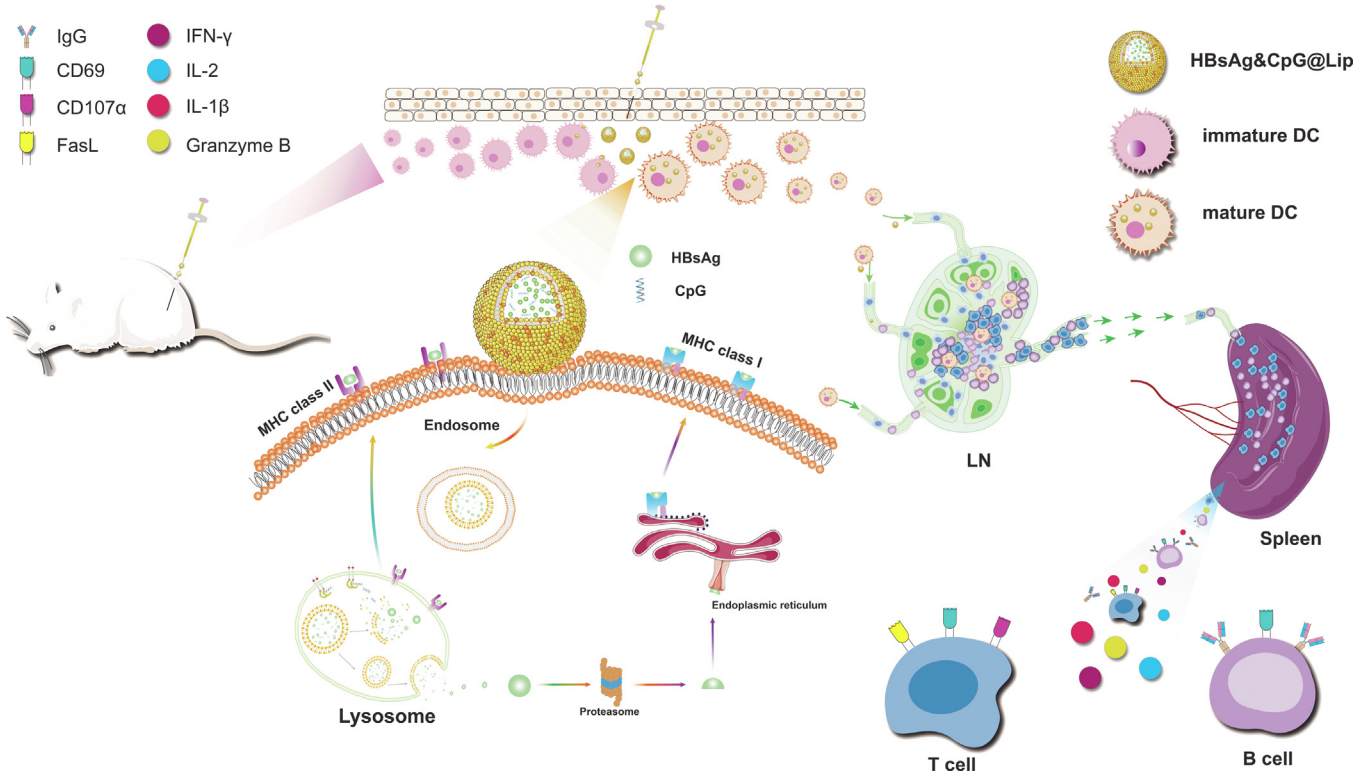

Fig. 7. Immunological mechanism of the HBsAg&CpG@Lip vaccination. With the assistance of the membrane fusion property, the antigen uptake/activation, cytosolic antigen release, and activation of lymph nodes were induced, promoting a prolonged and efficient humoral/cellular response. Reprinted from [278], Copyright (2020), with permission from Elsevier.

antigen-specific B cells with high affinity, thereby facilitating the maturation of plasma cells to cope with various virus subtypes.

Similar strategy is also meaningful for HPV prevention. As 70%–80% of cases of cervical cancer are caused by HPV-16 and HPV-18, these two types are potential candidates to achieve broader protection through cross-reactivity or expansion of the range of VLP types [282]. In this sense, the qualities of local *in vivo* concentration and potential effector cells (such as phagocytes or local memory B cells) also shape the cross-protection and longevity, which should be well tuned.

ii) Innovative delivery systems for $CD8^+$ T cell-based cross-protection are another promising strategy that is being exploited. Chahal et al. developed an adjuvant-free mono-dispersed dendrimer nanoparticle (MDNP, ~100 nm) vaccine platform wherein antigens were encoded by multiple mRNA replicons. After a single immunization, it elicited vital $CD8^+$ T and antibody responses that fully protected against lethal exposures to several deadly pathogens, including Ebola virus, H1N1 influenza, and *Toxoplasma gondii* [283]. This work may allow for rapid-response vaccines with broad efficacy, which could reduce the number and frequency of vaccinations and healthcare workers' burden.

In another notable example, Wang et al. encapsulated a STING agonist with pulmonary surfactant-biomimetic liposomes (PS-GAMP) in an attempt to accelerate the breadth of nonreplicating influenza vaccines towards universality. This PS-biomimetic nanoparticle has generated wide-spectrum cross-protection against distant H1N1 and heterosubtypic H3N2, H5N1, and H7N9 viruses as early as 2 days after a single intranasal immunization. The adjuvant had potent effects on both primary and booster immune responses, raising serum Ag-specific IgG1 10-fold, IgG more than 100-fold, and IgG2c ~ 1000-fold compared with VN04 H5N1 vaccine alone. The cross-protection lasted for at least 6 months, concurrent with durable lung $CD8^+$ resident T_{RM} cells in mice. These $CD8^+$ T_{RM} cells, rather than circulating memory $CD8^+$ T cells, contributed to the observed long-term protection as their function was not compromised by T cell egress inhibitor. That work strengthened the notion that even transient vaccine-activated innate immunity was sufficient to augment both humoral and cellular immune responses.

The intracellular delivery sites (lysosomal or non-lysosomal) and antigen processing (MHC I- or MHC II-mediated presentation) are crucial for cell-mediated response against most vaccine antigens, especially for viral infections and intracellular bacterial infections. The traditional process for exogenous antigens involves lysosomal degradation route and subsequent MHC II-medicated $CD4^+$ T cell priming (humoral response). Some extracellular bacteria (e.g., *S. pneumoniae*) are not capable of entering the cells, which is indispensable to the intracellular delivery manner. To prevent such bacterial infections, a higher titer of antibodies that can neutralize the pathogens is needed. In this case, the aim of vaccine delivery systems mainly include eliciting efficient antibody response through a Th2-biased immune response mechanism. In contrast, to cope with the intracellular bacteria (e.g., *S. typhi*) or most viruses (e.g., SARS-CoV-2, influenza) that are lethal or variable, cellular response ($CD8^+$ T priming) is particularly important for long-term or cross-protection. Therefore, the aforementioned cross-presentation delivery strategies (e.g., lysosomal escape and biomimetic membrane fusion) or delivery systems (e.g., pH-sensitive or positively charged synthetic particles/liposomes) should be designed to tune the intracellular fate (distribution and presentation) of exogenous antigens for $CD8^+$ T priming.

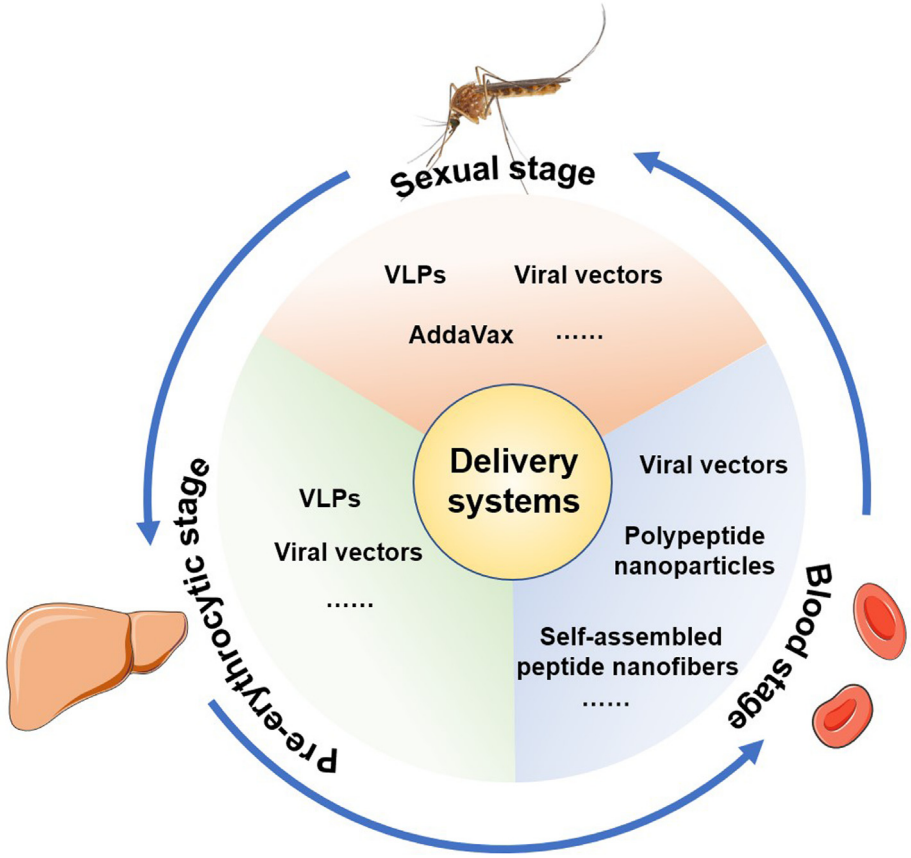

Fig. 8. Malaria parasite life cycle and delivery systems for vaccine development. The life cycle of malaria parasite contains three stages, including pre-erythrocyte stage, blood stage, and sexual stage. Many kinds of delivery systems have been explored for malaria vaccine design and have been developed to potential malaria vaccine candidates.

Table 5
Current malaria vaccines with delivery systems in clinical trials.

Vaccine candidate	Clinical trial registration number	Stage	Delivery system	Antigen(s)	Species and strain of malaria parasite	Adjuvants used
Pre-erythrocytic projects						
RTS,S/AS01E	NCT00866619	Phase III	VLP	Pf CSP (207–395)& HBsAg	*P. falciparum*	AS01E
RTS,S-AS01 fractional dose regimes	NCT02992119	Phase II	VLP	Pf CSP (207–395)& HBsAg	*P. falciparum*	AS01B / AS01E
ChAd63/MVA ME-TRAP	NCT01635647 (VAC050)	Phase I/ IIb	ChAd63, MVA	TRAP + ME epitopes (CS, LSA1, LSA3, STARP, EXP1, pb9)	*P. falciparum*	
ChAd63/MVA ME-TRAP +Matrix M™	NCT01669512 (VAC048)	Phase I	ChAd63, MVA	TRAP + ME epitopes (CS, LSA1, LSA3, STARP, EXP1, pb9)	*P. falciparum*	Matrix M™
CSVAC	NCT01450280	Phase I	ChAd63, MVA	CS	*P. falciparum*	
R21/Matrix-M1	NCT04704830	Phase III	VLP	CSP less- HBsA	*P. falciparum*	Matrix-M1
adjuv R21 (RTS,S-biosimilar) with ME-TRAP combined	NCT02905019	Phase I/ IIa	ChAd63, MVA	CSP less- HBsA + MeTRAPg	*P. falciparum*	Matrix-M1
Blood stage projects						
ChAd63 RH5 +/- MVA RH5	NCT02181088	Phase Ia	ChAd63, MVA	RH5	*P. falciparum*	
ChAd63/MVA PvDBP	NCT01816113	Phase Ia	ChAd63, MVA	PvDBP_RII	*P. vivax*	
Sexual stage projects						
Pfs25 VLP	NCT02013687	Phase I/ IIa	VLP	Pfs25	*P. falciparum*	Alhydrogel
ChAd63 Pfs25-IMX313/MVA Pfs25-IMX313	NCT02532049	Phase Ia	ChAd63, MVA	Pfs25	*P. falciparum*	

4. Parasitic infectious diseases and advanced delivery systems

Parasitic infections are highly prevalent worldwide, and many parasitic infectious diseases (such as malaria, schistosomiasis, and African trypanosomiasis) seriously threaten human health, especially in poor countries and regions. However, most of these diseases have usually been neglected. Among them, malaria, caused by *Plasmodium* (including P. *falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi*), is associated with high morbidity and mortality worldwide. The most lethal is malaria caused by *P. falciparum*, which is mainly distributed in sub-Saharan Africa. Vaccines are important in the prevention of malaria; according to the life cycle of *Plasmodium*, there are three stages suitable for developing a potential malaria vaccine [284]. The first one is the pre-erythrocyte stage, which may involve antibody response to prevent sporozoites from invading hepatocytes [285,286]. The second one is the blood-stage of the parasite. In this stage, red blood cell invasion could be controlled, resulting in fewer disease symptoms or asymptomatic infections [287,288]. However, the immunogenicity of some high-conservation protein antigens is very low [289–291]. The third stage is the stage of sexual parasite forms or gametocytes. Vaccines designed for this stage are intended to block the spread of malaria.

Many malaria vaccine delivery systems have been developed (Fig. 8), and some of them have been tested in clinical trials, including two kinds of delivery vehicles (Table 5). For example, vaccine based on VLP is the most advanced malaria vaccine in the pre-erythrocyte stage to date. By fusing a recombinant protein of the *P. falciparum* circumsporozoite protein (CSP) [286], containing known B- and T-cell epitopes [292], to the hepatitis B surface antigen (HBsAg), the expressed fusion protein could self-assemble into VLPs (designated RTS) that display the antigens on their surface [293]. A phase III study of the candidate vaccine RTS,S/AS01, which was studied from 2009 to 2014 in children in seven sub-Saharan African countries, revealed that vaccine efficacy against clinical malaria over 12 months after 3 doses was 56% in the 5–17 month age group and 31% in infants at the age of 6–12 weeks [294]. Although the efficacy against clinical malaria decreased over time and vaccinated children suffered increased risk of clinical malaria compared with controls after 5 years [294,295], malaria was prevented in young children who are usually at a high risk for severe malaria complications, and a booster dose could slow down the attenuation [296,297]. Although these candidate vaccines are often unable to induce higher antibody titers, there is great hope to prevent malaria in countries with limited resources, especially in children. In addition, some other delivery carriers, such as self-assembling polypeptide [298], self-assembled nanofibers [299], or some novel adjuvants like AddaVax (a squalene-based oil-in-water nano-emulsion) [300], have also been developed, which may provide more choices for the development of a malaria vaccine.

5. Fungal infectious diseases and advanced delivery systems

Currently, the incidence rate of fungal infections is increasing [301]. They often occur in individuals with weakened immune functions; some fungi can induce invasive fungal infections, with mortality rates of about 30%–40% [302]. Many kinds of fungal vaccines have been developed, but none were approved by FDA because patients with fungal disease generally have low immunity and are often unable to achieve effective response after immunization [303]. The Th1/Th17 profiles immunity can effectively prevent fungal infections [304].

Various delivery systems have been applied in antibacterial and viral vaccine studies, as described above. However, only a few vehicles have been used in antifungal vaccine design. For example, Chauhan et al. described an Escheriosomes-based delivery system to enhance the immune response to cytosolic antigens (cAg) of *Candida albicans,* an opportunistic human pathogen and the most common cause of fungal invasive infections [305]. When mice were immunized subcutaneously, a strong cellular immune response was induced, generating protective immunity (75% mice survived) against systemic *C. albicans* infection [306]. Furthermore, Carneiro et al. described another liposome, dioctadecildimethylammonium bromide: monoolein (DODAB:MO), consisting of DODAB and a stabilizer MO [307]. DODAB induced stronger cellular immune responses and has been used as a carrier in drug delivery studies [308–310]. By incorporating the cell wall surface proteins (CWSP) from *C. albicans* and subcutaneous immunization in mice, the DODAB:MO loaded with CWSP induced a strong specific Th1 immune response and protected 62.5% of mice from death of intravenous *C. albicans* infection [307]. De Bernardis et al. described a *C. albicans* vaccine (PEV7) by incorporating a truncated, recombinant aspartyl proteinase-2 of *C. albicans* into influenza virosomes, which were assembled *in vitro* from synthetic lipids and purified influenza virus envelope components. Following intravaginal route of immunization, this vaccine provided local, long-lasting mucosal immunity and protection against candida vaginitis [311].

Although there have been no further explorations of delivery systems against fungal infections, some promising vehicles, such as *L. lactis* particles and polymer micro/nanoparticles, could be tried because of their ability to induce a strong Th1/Th17 immune response.

6. Conclusions

Epidemic diseases have influenced the world throughout human civilization and even dictated the course of human history. Among treatment and prevention strategies, vaccination has played an irreplaceable role in saving people's lives. Nevertheless, high infection rates, widespread transmission, or high fatal ratio of outbreaks raise huge challenges for vaccine design. In this review, we summarized the major devastating issues of various epidemic pathogens (bacteria, viruses, fungi, and parasites), the latest clinical vaccine candidates (e.g., COVID-19 vaccine licensure), and the recent developments in antigen delivery systems for preventing infectious diseases. We particularly emphasized the design of the delivery systems for robust/high protection, long-term protection, or/and cross-protection. The corresponding delivery systems involve synthetic micro/nanoparticles (e.g., polymer and lipid particles), biological particles (e.g., exosomes and viral vectors), and integrated devices (microneedle patch), with a great potential to break through the barriers of traditional vaccines and adjuvants. These delivery concepts are not only adapted to the antiviral vaccines but are also applicable for the vaccines against bacterial infections and other infectious diseases. Although there have been few studies on fungal and parasite vaccine delivery systems, some exciting results about vaccine delivery encourage further research on that matter.

These delivery materials, mainly including inorganic, polymers, liposomes, and protein carriers, have their own advantages for different types of diseases. Generally, the best immune route is often the one that is similar to the pathogen's route in natural infection; hence, for intestinal and respiratory bacteria, the development of delivery vehicles suitable for mucosal routes is more attractive because they would stimulate both local and systemic immune responses. For example, for prevention of respiratory diseases by achieving effective respiratory tract mucosal immunity, materials with retention capacity and resistance to easy dilution and degradation are required. In this context, some advanced nanogels and

chitosan have suitable characteristics endowing them with very good immune response effects. In contrast, to reach the intestinal mucosa, a vaccine needs to pass through the extreme stomach environment, so additional protection of the delivery vehicle is often required. Probiotic carriers have unique advantages in this respect and can colonize the intestines; in addition, the protective effect of probiotic-based vaccine delivery systems against digestive tract diseases seems to be better than that against respiratory infections, which may not only be related to the characteristics of antigens but also to the fact that probiotic carriers are more suitable for the intestinal mucosa. Furthermore, compared with other immunization methods, oral vaccines have a higher safety threshold. Therefore, OMVs (containing lipid A and other components) of some digestive tract bacteria can also be used as oral vaccines, and they have shown good results in animal models.

In addition to the above-mentioned mucosal immunity, for some invasive infectious diseases, delivery vehicles such as biomimetic carriers, liposomes, and proteinaceous particles have great potential because they can stimulate humoral immune responses stronger than those achieved from non-mucosal immune routes, thereby providing complete protection from the lethal challenges. However, many promising delivery systems are rarely further validated in other bacterial species, which also is a feature of bacterial research. The reason of this phenomenon may be the wide variety of infectious disease pathogens and the relatively scattered research in the prophylactic vaccine field. In addition, it is also due to the differences in the cultivation requirements and evaluation methods of different bacteria and restrictions on acquisition and permission.

According to the existing data, vaccines can stimulate effective immune protection soon after vaccination. However, only a few carriers (such as probiotics and polyanhydride particles) have been studied for long-term immune protection. Some marketed vaccines, such as acellular pertussis vaccines, face the problem of a reduction in the protective effect over years, so it is necessary to further explore whether different delivery systems could help to overcome this issue.

7. Challenges and future directions

Recent vaccine delivery systems have helped to catalyze a series of vaccine candidates. However, there are still some challenges in the delivery system design for prophylactic vaccines. The first one involves the vaccine delivery system against multidrug resistant opportunistic pathogens that may seriously threaten special populations, such as older individuals, immunosuppressed persons, or patients before surgery. Therefore, an optimal delivery system should meet some important additional requirements (such as higher safety, rapid onset with only one immunization needed, and adequate protection), and special animal models (e.g., older animals) should be used for evaluation. The second one is carrier-induced epitope suppression (CIES) by proteinaceous delivery carriers, such as self-assembled proteinaceous nanoparticles, VLP, and viral vectors. CIES has been a great concern because the same carrier may result in the dampening of the effect of subsequent vaccination. Although it has been shown that CIES could be overcome by high coupling densities, repeated injections, and/or higher doses, this problem has not yet been fully solved. The third one is the development of delivery systems that endow vaccines with therapeutic efficacy for chronic infections, such as hepatitis B, tuberculosis, and brucellosis. Therefore, a new balance between the Th1 and Th2 response needs to be established. Finally, the balance between the rational design for specific protection demands and the safety/feasibility requirements for clinical translation should not be overlooked. In response to the demand for targeted delivery, immune regulation, or specific population (e.g., children or older persons), complex design strategies (e.g., targeting peptides, adjuvants) are usually involved. When the delivery system includes multiple components, the difficulty of the quality control/process optimization and even the biosafety consideration is augmented, which decreases the chances for further application. In particular, the outbreak of epidemic disease unprecedentedly narrows the development period and requires delivery platforms that cater to fatal pathogens in a timely manner.

In the future, the resolution of these challenges is indispensable to the renewal of biomaterials, the intelligent design of delivery systems, the exploration of immunological mechanisms, and the assistance of innovative technology. First, the renewal of biomaterials with intelligent design, especially for the pathogen-mimicking systems (e.g., biologically derived exosomes or synthetic chassis), will help to prevent vaccine resistance or endow vaccines with the expected immunological response. An optimum delivery system (e.g., temperature-sensitive hydrogels or hollow porous MPs) can be applied to extend the administration route (e.g., nasal or inhalation vaccination) and functions at the initial site of pathogen invasion. In particular, by mimicking the physiochemical properties (e.g., mobility and deformability) or intracellular behavior (e.g., lysosomal escape pathway) of microorganisms, robust immune response or high CTL cross-protection is realized.

Second, to maximize protection and avoid ineffective responses, it is important to design individualized vaccine delivery systems depending on the pathogen's characteristics (invasive or noninvasive; intracellular or extracellular) and the underlying immunological mechanisms. The delivery system can be designed to activate local innate responses that translate into the mucosal immunity (e.g., generation of secretory IgA or high-avidity CTL at mucosal sites). In addition, efficient delivery systems can be developed upon the novel theoretical mechanisms to address specific demands (e.g., a decrease of the pre-existing immunity of adenovirus vaccination, or eliciting the protection rate among older individuals).

Third, a combinatorial library of antigens, adjuvants, or delivery materials (e.g., lipids) is available, and the top candidate with specific merits can be screened promptly with the assistance of novel technology (e.g., nanotechnology and artificial intelligence). For example, the distribution route (e.g., cell membrane or acidic lysosome) and ultimate fate (e.g., enzyme degradation or ligand–receptor-based activation) of each component can be calculated and predicted. In this context, a delivery system can be designed for maximum immune efficiency in a coupled spatio-temporal manner. In addition, with the assistance of computers and artificial intelligence, more modules (even including special functions) will likely be designed to assemble a potentially enormous diversity of nanovaccine structures, which is expected to solve the problem of CIES of protein carrier vaccines.

Epidemic diseases have influenced the world throughout human civilization and even dictated the course of human history. Vaccine delivery strategies have been deeply studied in many fields, and their importance in the prevention of infectious diseases has become increasingly prominent. Although most of the advanced delivery systems are still in the laboratory research stage, several products have entered clinical trials or helped to catalyze a series of vaccine candidates, which should lead to advanced prophylactic vaccination with balanced safety and efficacy in the future. Due to the unparalleled need for vaccines globally, this field will continue to blossom in the prevention of infectious diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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