Computational and Structural Biotechnology Journal 29 (2025) 259–270

Contents lists available at ScienceDirect

Computational and Structural Biotechnology Journal

journal homepage: www.elsevier.com/locate/csbj

Review Article

Advances in the structure-based design of protein vaccines for respiratory infectious diseases

Xiaotian Tie [a,b,1], Jiaxuan Li [a,c,1], Hao Wu [a,c], Ruiqi Weng [c], Yanjun Zhang [b,*], Jianhua Li [b,*], Keda Chen [c,*]

[a] Zhejiang Chinese Medical University, Hangzhou 310053, PR China
[b] Zhejiang Key Laboratory of Public Health Detection and Pathogenesis Research, Department of Microbiology, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, P. R. China
[c] Key Laboratory of Artificial Organs and Computational Medicine in Zhejiang Province, Shulan International Medical College, Zhejiang Shuren University, Hangzhou, PR China

ARTICLE INFO

Keywords:
Respiratory diseases
Influenza
RSV
SARS-CoV-2
Structure-based design
Protein vaccines

ABSTRACT

Respiratory infectious diseases are among the leading causes of morbidity and mortality worldwide, particularly affecting children, older adults, and immunocompromised individuals. Traditional vaccine development approaches face limitations in addressing the rapid mutation and immune evasion mechanisms of respiratory pathogens. In recent years, structure-based protein vaccine design has emerged as a critical direction in vaccine research. This strategy utilizes the three-dimensional structural information of key pathogenic antigens, combined with reverse vaccinology, computational biology, and protein engineering to optimize antigen design and enhance immunogenicity. This review summarizes recent progress in structure-based protein vaccine development for major respiratory pathogens, including influenza viruses, respiratory syncytial virus (RSV), and coronaviruses such as SARS-CoV-2. We highlight innovative vaccine platforms, including antigen optimization strategies, nanoparticle-based vaccines, and novel adjuvant development. Additionally, we discuss the major challenges in vaccine development—such as antigenic variability, immune durability, and large-scale manufacturing—and propose future directions for research and application.

1. Introduction

Over the past few decades, respiratory infectious diseases have remained a major threat to global public health [1], particularly those attributable to influenza viruses, respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These viruses disproportionately affect vulnerable populations such as children, the elderly, and individuals with weakened immune systems, resulting in elevated rates of hospitalization and mortality [2]. Since its emergence in late 2019, SARS-CoV-2 has exhibited rapid global transmission, causing a global pandemic. It is transmitted via droplets, direct contact, and aerosols [3], and can involve multiple organ systems, including the pulmonary, cardiovascular, neurological, and gastrointestinal systems [4]. In contrast, influenza viruses undergo frequent antigenic variation, resulting in seasonal epidemics and considerable challenges for vaccine development. Although current influenza vaccines reduce infection rates and the severity of complications [5,6], their protective efficacy remains suboptimal due to antigenic drift and shift [7]. Meanwhile, RSV remains a leading cause of severe respiratory illness to infants and the elderly. Despite the availability of monoclonal antibodies for high-risk infants,a safe and broadly effective vaccine is still lacking [8,9]. Studies suggest that coinfection with SARS-CoV-2, influenza, and RSV can exacerbate illness severity and increase hospitalization and ICU admission rates [10,11].

Among various vaccine development strategies, protein subunit vaccines are attracting growing interest for their distinct advantages. Compared with inactivated, live-attenuated, and mRNA-based vaccines, protein vaccines utilize purified and structurally optimized antigen components [12, 13],significantly reducing the risks of genetic reversion [14] or adverse immune responses,This makes them particularly suitable for high-risk populations such as infants, the elderly, and immunocompromised patients. Protein vaccines also demonstrate superior

* Corresponding authors.
E-mail addresses: yjzhang@cdc.zj.cn (Y. Zhang), jhli@cdc.zj.cn (J. Li), chenkd@zjsru.edu.cn (K. Chen).
[1] These authors have contributed equally to this work and share the first authorship.

https://doi.org/10.1016/j.csbj.2025.10.008
Received 18 June 2025; Received in revised form 27 September 2025; Accepted 3 October 2025
Available online 9 October 2025

stability and reduced reliance on cold-chain infrastructure [14,15], facilitating distribution and administration in resource-limited settings. Furthermore, through rational antigen design and adjuvant pairing, protein vaccines can precisely modulate both humoral and cellular immune responses. [16],The use of nanoparticle platforms further augments immunogenicity, cross-protection, and immune durability. Structure-based design of protein vaccines has emerged as a pivotal approach, leveraging structural biology, computational tools [17], and protein engineering to optimize antigen conformation, improve epitope exposure, and promote broad-spectrum immunity [6]. Recent innovations—such as nanoparticle-based delivery systems [18,19], optimized adjuvants, and new vaccine platforms—hold promise for improving vaccine durability, cross-protective efficacy, and scalable production [20]thereby providing a strong foundation for the advancement of respiratory virus vaccine development.

This strategy leverages three-dimensional structural information of key pathogen antigens combined with reverse vaccinology and computational optimization to design stable and more immunogenic antigens that enhance vaccine protective efficacy [21] Prefusion stabilization—by limiting S2 folding and S1 shedding—preserves native-like epitope landscapes and improves neutralizing antibody responses. For coronaviruses, Pallesen et al. and Wrapp et al. first reported that introducing double-proline substitutions in the S2 hinge region could maintain the spike protein in its prefusion conformation, thereby preserving critical neutralizing epitopes and enhancing immunogenicity [22, 23], In RSV vaccine research, McLellan et al. and Krarup et al. pioneered the structural determination and stabilization of prefusion F proteins (such as DS-Cav1), which markedly increased neutralizing antibody responses [24,25]. In addition, innovations in antigen-display platforms, such as nanoparticle vaccines and virus-like particles (VLPs), offer new solutions to enhance antigen stability, optimize B-cell recognition, and improve antibody responses [26,27]. In particular, structure-guided approaches have shown three main pathways to counteract rapidly evolving pathogens: (i) conserved-site focusing—masking immunodominant yet highly variable epitopes while preferentially exposing conserved regions such as the HA stem or S2 subunit; (ii) mosaic/multivalent display—co-presenting antigens from multiple strains on ordered arrays such as I53–50 or mi3 nanoparticles to broaden lineage coverage; and (iii) consensus/lineage coverage—using deep-sequence information to predesign antigens that optimize cross-reactivity and drift tolerance."

In addition,the optimization and application of vaccine adjuvants is also a crucial approach to enhance the immunological efficacy of protein vaccines. While traditional aluminum salt adjuvants can boost antibody responses, they have limitations in terms of cellular immunity [28–30]; In contrast, mature non-aluminum-based adjuvants (such as MF59, AS01, and AS03) have achieved broader and more durable immune responses by promoting antigen presentation and the activation of immune cells. In recent years,combination adjuvants [30] and nanoparticle delivery systems further expand the immunogenic potential of protein vaccines, providing a systematic framework for addressing viral variation.

Against this backdrop,this review will explore structure-based design of protein vaccines, with an emphasis on recent advances in antigen optimization strategies, the application of nanoparticle vaccines, and the optimization of adjuvants. At the same time, It will also highlight key challenges in vaccine development, such as immune durability, breadth of protection, and scalability, and discussing potential future directions for advancing respiratory virus vaccine strategies.

2. Structure-based design of protein vaccines

2.1. Antigen optimization strategy

The immunogenicity of protein vaccines largely depends on the structural refinement of antigens to ensure their efficient recognition by the immune system and the induction of a robust immune response [31]. Traditional protein vaccines typically use full-length or subunit antigens, but this approach has inherent limitations. In some pathogens, key epitopes are immunologically concealed—shielded by native folding or extensive glycosylation—making it difficult to elicit potent neutralizing antibodies, as exemplified by glycan shielding on HIV-1 Env and influenza hemagglutinin [32]. Moreover, certain pathogens, such as influenza viruses and coronaviruses, frequently undergo antigenic drift and shift following infection, thereby diminishing the protection conferred by vaccine-induced immunity. Consequently, a central challenge in protein vaccine development lies in optimizing the three-dimensional structure of antigens so that they not only mimic the native conformation of the pathogen but also expose key epitopes, thus inducing a robust and durable immune response.

In recent years, antigen optimization strategies based on structural biology have made significant breakthroughs, with three-dimensional conformational stabilization emerging as a central technique. For instance, during the development of SARS-CoV-2 vaccines, researchers discovered that the spike (S) protein in its pre-fusion conformation is substantially more immunogenic and capable of eliciting potent neutralizing antibodies. In contrast, the post-fusion conformation results in structural rearrangements that mask key epitopes, thereby reducing immunogenicity. By introducing stabilizing mutations such as the double-proline (2 P) substitutions into the S2 hinge region [22], the pre- to post-fusion conformational transition can be restricted and S1 shedding minimized, thereby preserving the native-like prefusion epitope landscape and immunogenicity; this approach was subsequently extended to multi-site stabilization exemplified by HexaPro (6 P) [33], and has since been validated and widely implemented across both mRNA and recombinant protein vaccine platforms.This strategy has been successfully applied to various vaccines,(such as BNT162b2 [34], mRNA-1273 [35]).

It is noteworthy that the elucidation of spike/fusion glycoprotein structures and the stabilization of their prefusion conformations were not isolated discoveries of the COVID-19 era but rather rapid extensions of a series of landmark studies. Pallesen et al. [22] established the principle of "prefusion conformation–targeted" design in coronavirus spike research, and Wrapp et al. [23] subsequently resolved the prefusion structure of the SARS-CoV-2 spike by cryo-electron microscopy and demonstrated that the 2 P stabilization preserves key neutralizing epitopes in their native presentation, thereby directly facilitating the rapid translation of 2 P/6P-engineered antigens into mRNA and recombinant protein vaccines. A similar structure-guided paradigm has also achieved breakthroughs in other respiratory virus vaccines: the DS-Cav1 prefusion F protein design proposed by McLellan et al. [36] for RSV not only markedly enhanced neutralizing antibody responses but also reduced the risk of enhanced respiratory disease (ERD) historically associated with non-ideal antigen conformations, providing a model of both safety and efficacy for prefusion antigens. The influenza vaccine field has likewise benefited from structural guidance, with hemagglutinin (HA) stem-focused immunogen design and mosaic or multivalent HA displays on ferritin/self-assembling nanoparticles (such as I53–50 or mi3) demonstrating in multiple animal and early clinical studies expanded lineage coverage and the promotion of high-affinity memory B-cell maturation, thereby improving cross-neutralization of influenza A and B viruses [26], while structural studies on influenza C are also under way. Collectively, these landmark investigations constitute a transferable design paradigm of "native-like prefusion conformation preservation → structure-based epitope engineering → high-density, ordered nanoparticle display," providing a robust theoretical and practical framework for combating highly variable respiratory pathogens [37].

In China, the Recombinant SARS-CoV-2 Vaccine (CHO Cell), marketed as "LiKang V-01" and developed under the leadership of Academician Gao Fu, employs a dimeric receptor-binding domain (RBD) strategy. It was approved for emergency use by the National Medical Products Administration (NMPA) in 2022 and has completed Phase III clinical trials across multiple countries, demonstrating favorable safety profiles and broad-spectrum protection against circulating variants [38]. By linking two RBD units into a stable dimeric configuration, the vaccine enhances the conformational stability of the antigen and its recognition by B cells, thereby amplifying neutralizing antibody responses [38]. In the case of RSV vaccines, early structure-based work by McLellan et al. identified and stabilized the prefusion conformation of the RSV fusion (F) protein (DS-Cav1), which showed markedly improved immunogenicity in animal models [25,38]. This prefusion F antigen design underpins the recent FDA-approved vaccines developed by GSK (RSVPreF3) and Pfizer (RSVpreF), which incorporate stabilized prefusion F proteins to elicit strong neutralizing responses and demonstrated significant efficacy in high-risk populations, including the elderly and pregnant women for infant protection [39,40].

In addition to optimizing three-dimensional structures, enhancing antigen display platforms has become a critical focus in protein vaccine development. Traditional protein vaccines typically present antigens as monomers or dimers; however, these conformations may not efficiently stimulate B cell recognition or induce a strong immune response. To overcome this challenge, researchers have developed nanoparticle-based antigen display technologies, which enable antigens to be presented in a highly ordered and multivalent configuration. For instance, the I53–50 nanoparticle platform can efficiently display viral trimeric antigens, such as the influenza virus HA trimer [41]or SARS-CoV-2 RBD [42,43], thereby significantly enhancing B cell recognition and improving antibody affinity and potency. Furthermore, ferritin-based nanoparticles (ferritin NPs) have been widely utilized in the development of vaccines for influenza [44,45], RSV, and coronaviruses. These self-assembling nanoparticles uniformly display antigens on their surface, mimicking the natural form of viral particles and enhancing the immune system's recognition and response.

Building on this, antigen grafting strategies offer a novel approach for broad-spectrum protection in protein vaccines. Certain respiratory viruses, such as influenza viruses and coronaviruses, contain conserved domains outside of highly variable antigenic regions, like the influenza HA head and SARS-CoV-2 RBD. Although the immunogenicity of these conserved domains is generally low, they can be optimized in vaccine design to improve cross-protection. For example, in influenza vaccine development, researchers have removed the variable HA head region, retaining only the highly conserved HA stem region (HA-stem), and grafted it onto a self-assembling protein platform, thereby effectively inducing a broad-spectrum immune response against different influenza subtypes [46–48]. Similarly, the mosaic RBD nanoparticle vaccine improves cross-protection against SARS-CoV-2 variants by grafting RBD fragments from different variants onto nanoparticles [42,43,49]. These strategies address the issue of immune escape caused by rapid viral mutations, providing a safeguard for the long-term efficacy of vaccines.

As antigen optimization strategies continue to evolve,researchers have gradually explored more efficient vaccine delivery systems to enhance immunogenicity, prolong immune persistence, and broaden cross-protection. Among these, nanoparticle vaccines have emerged as a promising new platform in recent years. By mimicking the antigen presentation of natural viral particles, they significantly enhance vaccine-induced immune responses and have become a central focus in the research of vaccines for respiratory infectious diseases. In addition, the structural stability of nanoparticle vaccines provides greater adaptability during transportation and storage, reducing dependence on cold-chain logistics and offering feasibility for large-scale vaccination.

The nanoparticle vaccine platform encompasses various types, including self-assembling protein nanoparticles, artificially synthesized nanomaterial carriers, and virus-like particles (VLPs). Researchers are exploring ways to further optimize the physicochemical properties of nanoparticles to improve their biocompatibility and antigen delivery efficiency. Moreover, the combination of nanoparticles with novel adjuvants has become a new trend in vaccine development, allowing for enhanced immune responses while reducing the required vaccine dose, thereby lowering production costs. Overall, with their unique advantages, nanoparticle vaccines are expected to become a vital direction in future vaccine development and play a greater role in the prevention and control of respiratory infectious diseases.

As traditional structure-based optimization methods continue to mature, AI-driven approaches are now accelerating the iterative advancement of antigen design. In addition to the strategies described above, artificial intelligence has emerged as a powerful driver of structure-based vaccinology, enabling faster translation of antigen optimization. Deep learning–based immunoinformatics tools (such as IEDB and VaxiJen) integrate human MHC polymorphism data to accurately predict the immunogenicity and cross-reactivity of B- and T-cell epitopes. For example, in influenza vaccine research, AI analysis of thousands of HA sequences has identified highly conserved neutralizing epitopes in the stem region, providing targets for broadly protective vaccine design [50]; for SARS-CoV-2, AI can predict epitope drift in variant RBDs and assist in designing mosaic antigens covering Omicron and related sublineages [51]. In structural modeling, tools such as AlphaFold3 and Rosetta enable high-accuracy de novo prediction of key antigen conformations, overcoming limitations of traditional structural methods; Wrapp [23]elucidated the prefusion conformation of the SARS-CoV-2 spike and its ACE2-binding interface, providing a basis for the double-proline stabilization,while McLelln [24] identified key conformational sites in the RSV F protein and designed the DS-Cav1 stabilized variant. Machine-learning approaches can also analyze sequence–structure–function relationships to select mutations that enhance antigen thermal stability and expression; Pallesen [22] showed that optimized spike variants expressed at higher levels in CHO cells and elicited stronger neutralizing responses than the wild type. Collectively, these AI-driven tools shorten antigen-design timelines, reduce experimental costs, and offer a transferable framework for developing broadly protective vaccines against highly variable respiratory pathogens such as SARS-CoV-2, RSV, and Influenza.

2.2. Nanoparticle vaccine

With the continuous advancement of vaccine antigen design concepts, the application of nanoparticle technology in vaccine development has become increasingly widespread. In particular, in the field of respiratory infectious disease prevention and control, nanoparticle vaccines have emerged as one of the most promising vaccine platforms due to their excellent antigen presentation capabilities and structural stability. By presenting antigens in a multivalent form and arranging them multivalently on the surface of nanoparticles, these vaccines can not only more effectively activate B cells and T cells [52,53], but also mimic the spatial configuration of natural viral particles, significantly enhancing the immune system's ability to recognize antigens. Compared to traditional protein vaccines, nanoparticle vaccines exhibit superior performance in inducing potent neutralizing antibodies, enhancing cross-protection [54],and promoting the formation of immune memory [55].

Currently, structure-based nanoparticle vaccine platforms primarily include three major categories: ferritin self-assembling nanoparticles, I53–50 composite protein nanoparticles, and mi3 mosaic-type nanoparticles (Fig. 1). Each of these platforms has distinct characteristics, featuring either widely sourced, highly stable, and easily modifiable natural protein scaffolds, or artificially designed systems with sophisticated structural design and flexible antigen arrangement. The following sections will introduce the application and research progress of these three nanoparticle platforms in the development of vaccines against respiratory pathogens such as SARS-CoV-2, influenza virus, and RSV. The focus will be on analyzing their antigen presentation strategies, immune responses, as well as preclinical or clinical trial data, highlighting their unique advantages in enhancing vaccine immunogenicity and broad-spectrum protection(Table 1).

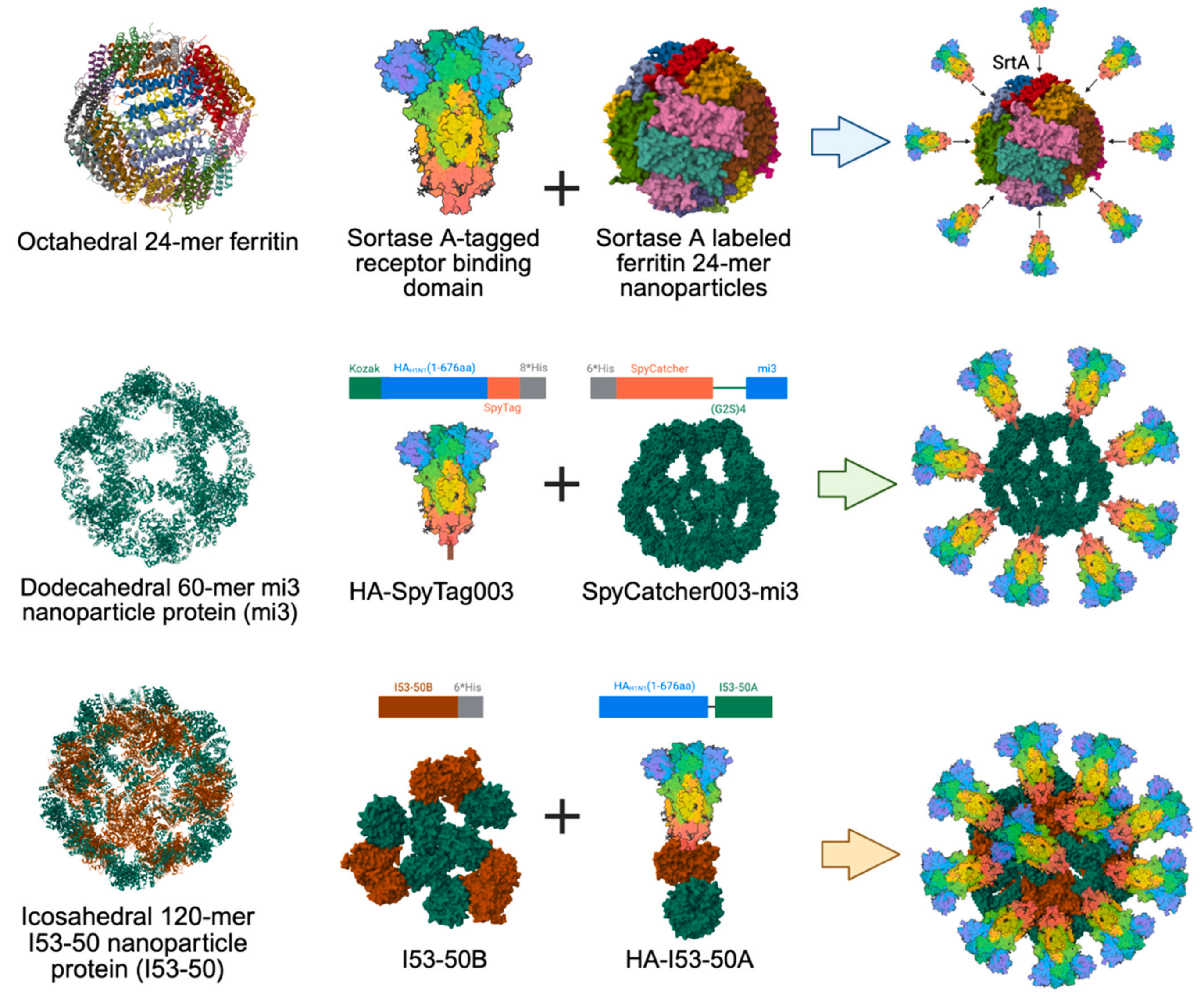

Fig. 1. Application of nanoparticle vaccine platforms. Illustration of ferritin, I53–50, and mi3 nanoparticles used in respiratory virus vaccines to enhance antigen presentation and immunogenicity through multivalent display.

2.2.1. Ferritin nanoparticle vaccine

Ferritin is a ubiquitous iron-storage protein found in bacteria, fungi, plants, and animals [56,57]. Its hollow 24-mer architecture confers high thermal and chemical stability—ferritin assemblies remain intact up to ~85 °C and resist denaturation under neutral pH—making ferritin an attractive platform for multivalent antigen display [58]. This property makes ferritin an ideal vaccine platform, capable of stably carrying antigens while preserving their immunogenicity [58]. Moreover, ferritin's three-axis symmetry is particularly well-suited for displaying trimeric antigens [59], such as influenza hemagglutinin (HA), the SARS-CoV-2 spike protein (S), and the RSV fusion protein (F).

In SARS-CoV-2 vaccine research, ferritin nanoparticles have been applied to optimize antigen display. For example, one study used the SpyCatcher/SpyTag system to covalently attach the SARS-CoV-2 receptor-binding domain (RBD) to the ferritin surface; the nanoparticle vaccine induced higher levels of neutralizing antibodies and stronger cellular immune responses than a monomeric S protein vaccine, and provided durable protection in a rhesus macaque model [60]. Another study presented the S protein trimer on ferritin nanoparticles to optimize antigen structure and enhance immunogenicity; the resulting SpFN vaccine elicited robust cellular and humoral responses in animal experiments and significantly reduced post-infection lung pathology [61]. In influenza vaccine research, ferritin nanoparticles have also shown marked advantages. Given the high variability of influenza viruses, traditional vaccines often fail to provide long-lasting, broad protection. Studies have demonstrated that by coupling influenza HA antigens to ferritin via self-assembly, highly effective nanoparticle vaccines can be produced; in animal models, these vaccines induced broadly neutralizing antibodies [50]. Furthermore, researchers have displayed the HA stem region of H1N1 on ferritin surfaces to enhance long-term protection against influenza. A Phase I clinical trial (NCT03186781) evaluating a novel (H2HA-ferritin) nanoparticle influenza vaccine platform reported good safety and potent neutralizing antibody induction, indicating broad protective potential [62]. In RSV vaccine research, ferritin nanoparticles have been used to display pre-fusion F protein variants. Studies show that multivalent antigen display on ferritin nanoparticles can effectively mimic native viral architecture, significantly improving vaccine immunogenicity and protective efficacy [41]. For example, one study presented the RSV G protein S177Q mutant on ferritin nanoparticles; this vaccine induced stronger neutralizing antibody responses, reduced viral loads in mouse models, and enhanced immune memory [63]. These results demonstrate

Table 1
Nanoparticle-based vaccine platforms and their immunological characteristics.

Nanoparticle Platform	Immunogen	Proposed Mode of Action	Licensed Vaccine Components	Immune Effect
Ferritin-based nanoparticles	Influenza HA, SARS-CoV−2 Spike protein, RSV F protein.	Self-assembly into 24-mer cages displaying trimeric antigens; enhances BCR crosslinking and antibody responses [105].	Vaccines against influenza, COVID−19, RSV.	Induces potent neutralizing antibodies and robust T cell responses [105,106]; SpFN showed strong immunogenicity in phase I trials.
I53–50 Nanoparticles	Influenza HA trimers, SARS-CoV−2 RBD trimers, RSV F protein.	Artificial two-component icosahedral scaffold; presents antigens densely and uniformly.	Applied in multivalent influenza and COVID−19 vaccines ;	Inducing neutralizing antibodies and T cell responses significantly enhances immune effectiveness [107].
MI3 Nanoparticle	SARS-CoV−2 RBD, Influenza HA	Ultra-stable 60-mer displaying diverse antigens via SpyTag/SpyCatcher	Mosaic vaccines for SARS-CoV−2, influenza.	Induces broad neutralizing antibodies against multiple sarbecoviruses and viral variants [107].
E2 nanoparticle	HIV Env, Influenza HA, RSV F antigen fragments	Virus-like particle presenting multivalent antigens; enhances B cell activation	Experimental HIV, influenza, RSV vaccines.	Strong B cell activation and antibody generation in preclinical studies [108].
SpyCatcher/SpyTag decorated nanoparticles	RBD, Spike, HA, F protein, etc.	Covalent attachment of antigens for stable, high-density display	Flexible system combined with various scaffolds (Ferritin, mi3, I53–50)	Improves antibody affinity, breadth, and durability; effective protection against SARS-CoV−2 [107].
Mosaic nanoparticles	Antigens from diverse strains (different variant RBDs or HA heads)	Co-display of diverse antigens on one particle to induce cross-protection	Universal vaccines against SARS-CoV−2 variants and influenza	Enhances cross-neutralization and protects against heterologous infections in animal models [109].
Lipid Nanoparticles (LNPs)	mRNA encoding SARS-CoV−2 Spike protein; Influenza HA; RSV F protein (in preclinical mRNA vaccines)	Encapsulate nucleic acids to protect antigens and enhance cellular uptake	BNT162b2 (Pfizer/BioNTech); mRNA−1273 (Moderna); mRNA influenza/RSV vaccines (in development)	Robust neutralizing antibodies and T cell responses; rapid scalability.
Virus-Like Particles (VLPs)	Recombinant SARS-CoV−2 Spike or RBD; RSV F pre-fusion protein; Influenza HA	Mimic viral geometry for dense, repetitive epitope display	NVX-CoV2373(Novavax); Ferritin/mosaic HA nanoparticles; RSV pre-F VLPs (clinical trials)	Broadly neutralizing antibodies, cross-lineage protection, enhanced immunogenicity.

the feasibility and advantages of ferritin nanoparticles as an RSV vaccine platform.

2.2.2. I53-50 composite nanoparticle vaccine

The I53–50 composite nanoparticle is another widely studied nanoparticle vaccine platform. This platform consists of two self-assembling protein subunits, I53–50A and I53–50B, which together form a stable icosahedral structure capable of efficiently displaying trimeric viral antigens [64] Compared to traditional monovalent antigen vaccines, the I53–50 nanoparticle allows multivalent arrangement of antigens on a single particle surface, thereby significantly enhancing B cell cross-linking activation and improving the potency of the antibody response [65]. In SARS-CoV-2 vaccine research, the RBD-I53–50 nanoparticle vaccine induced neutralizing antibody titers in mouse models that were ten times higher than those induced by monomeric antigen vaccines, and extended the duration of antibody responses to over three months [66–68], demonstrating exceptional immunogenicity. Furthermore, researchers utilized the SpyTag-SpyCatcher system to construct three different RBD nanoparticle vaccine candidates:RBD-Ferritin (24-mer), RBD-mi3 (60-mer), and RBD-I53–50 (120-mer) [67]. Animal studies showed that all three nanoparticle vaccines significantly enhanced antibody titers and cellular immune responses, with the I53–50 platform inducing the most robust immunological effects [68]. In influenza vaccines, one study demonstrated that an I53–50-based quadrivalent influenza nanoparticle vaccine could elicit broader neutralizing antibodies than existing influenza vaccines and effectively protect animals against infections from different influenza virus subtypes [69]. This strategy offers a new approach for the future development of universal influenza vaccines. Another research team used a baculovirus expression system in insect cells to produce recombinant HA5-I53_dn5B, which was assembled in vitro with I53_dn5A produced in a prokaryotic expression system to form a nanoparticle vaccine. The study found that immunization with the self-assembling nanoparticle-based HA vaccine induced significant levels of neutralizing antibodies in experimental animals. The research also showed that this nanoparticle-based HA vaccine could stimulate immune responses against various influenza virus subtypes, including H1N1 and H3N2 [70]. In the progress of RSV vaccine research, In the 1960s, a formalin-inactivated RSV vaccine (FI-RSV) caused enhanced respiratory disease (ERD) in infants, leading to increased hospitalization and mortality. This adverse outcome was attributed to the post-fusion conformation of the F protein presented by the inactivated vaccine, which lacked key neutralizing epitopes and instead elicited low-affinity, non-neutralizing antibodies together with a Th2-biased immune response, thereby exacerbating inflammation upon natural infection.Building on this historical lesson, structural biology studies resolved the prefusion conformation of the RSV F protein and enabled the design of stabilized antigens such as DS-Cav1. [71]. This nanoparticle platform had previously been shown to enhance the immunogenicity of influenza and Epstein-Barr virus (EBV) vaccines [27, 72]. The dual-component nature of the nanoparticle scaffold enables the production of highly ordered, monodisperse immunogens that present DS-Cav1 at a controlled density [73]. Experimental results showed that These antigens preserve the native-like prefusion epitope landscape, elicit high-titer and broadly neutralizing antibodies, and shift the immune response toward neutralizing antibodies and Th1-type immunity, thereby reducing the risk of ERD. This strategy illustrates the logic of “structure-guided immunogen design”: by maintaining the authentic prefusion epitope architecture and controlling immune polarization, it is possible to enhance vaccine efficacy while ensuring safety.

2.2.3. Mi3 mosaic nanoparticle vaccine

The mi3 mosaic nanoparticle is another important antigen delivery platform that has been widely applied in the development of coronavirus and influenza virus vaccines. What distinguishes the mi3 nanoparticle is its ability to incorporate antigens from multiple variants onto the same particle surface through precise design, thereby enhancing the breadth of vaccine protection. This strategy has proven particularly effective against SARS-CoV-2 variants. By integrating receptor-binding domains (RBDs) or spike protein antigens from different variants, mi3 nanoparticle vaccines can induce broader neutralizing antibody responses and provide robust protection against multiple variants.In SARS-CoV-2 vaccine research, scientists utilized the mi3 nanoparticle platform to fuse the spike protein (HexaPro) from the prototype strain and three variants of SARS-CoV-2 to the trimeric I53–50A, forming a tetravalent mosaic nanoparticle vaccine. Animal studies showed that this vaccine induced strong neutralizing antibody responses against multiple variants and provided broad-spectrum immune protection [74,75]. Additionally, researchers employed mi3 nanoparticles to present RBDs derived from both human and animal coronaviruses. The results indicated that, compared to homotypic nanoparticles, mosaic RBD nanoparticles could elicit more robust cross-reactive antibodies, thereby enhancing protection against SARS-CoV-2 and other Sarbecoviruses, such as SARS-CoV-1 and bat coronaviruses [75]. Similarly, in influenza vaccine development, the mi3 platform has been used to display conserved epitopes of the influenza virus matrix protein M2 (M2e) or fusion antigens from multiple HA subtypes, thereby triggering broad-spectrum immune responses against different subtypes such as H1N1 and H3N2. For example, single-component self-assembling nanoparticles (SApNPs) displaying the M2e epitope can provide long-lasting cross-protection after a single immunization [76], while multivalent HA nanoparticle vaccines can achieve full protection against both influenza A and B viruses through synergistic antibody and T cell responses [77].

2.2.4. *Lipid nanoparticles (LNPs) and virus-like particles (VLPs)*

Alongside advances in antigen optimization, innovations in delivery and presentation platforms have become key to enhancing vaccine immunogenicity. Lipid nanoparticles (LNPs), composed of ionizable lipids, cholesterol, phospholipids and PEG-lipids, protect and deliver nucleic acid or protein antigens at the nanoscale, improving cellular uptake and antigen presentation efficiency. During the COVID-19 pandemic, LNP-encapsulated mRNA vaccines such as BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) were rapidly authorized and demonstrated high immunogenicity and large-scale manufacturing feasibility in clinical trials [78,79]. Virus-like particles (VLPs) mimic the geometry and surface conformation of viruses without containing genetic material, enabling highly ordered, repetitive display of antigenic epitopes and markedly enhancing B-cell receptor cross-linking and neutralizing antibody induction. Ferritin-based and mosaic HA nanoparticles for influenza [27,50] have shown broad cross-protection in animal models, and Novavax's RSV F protein nanoparticle vaccine demonstrated enhanced immunogenicity and good tolerability in phase II/III trials [80]. By combining efficient antigen delivery (LNPs) with dense, ordered epitope presentation (VLPs), these platforms are driving the translation of vaccines against SARS-CoV-2, RSV and influenza from laboratory research to clinical application.

In summary, nanoparticle vaccines have demonstrated significant advantages in antigen presentation, structural stability, and immunogenicity, making them a major focus in the development of vaccines against SARS-CoV-2,influenza,and RSV.In the future, with continued advancements in antigen design and adjuvant optimization, nanoparticle-based platforms are expected to further enhance the breadth, durability, and cross-protective capabilities of vaccines, offering a powerful solution to combat the ongoing challenge posed by rapidly mutating viruses.

3. Optimization and application of adjuvants

Due to the inherently low immunogenicity of protein vaccines, adjuvants are often required to elicit a sufficient immune response. Therefore, the optimization and application of adjuvants have become critical steps in enhancing the efficacy of protein vaccines during their development. Currently approved adjuvants for human vaccines include MF59, water-in-oil emulsions, AS01, and CpG1018, each demonstrating distinct advantages in various vaccine formulations. For example, MF59 [81] a water-in-oil emulsion, has been widely used in influenza vaccines; its mechanism involves enhancing the effective presentation of antigens, thereby promoting B cell activation and antibody production [82,83], which significantly boosts the overall immune response.During the COVID-19 (coronavirus disease 2019) pandemic,a Phase I clinical trial in Australia evaluating a SARS-CoV-2 subunit vaccine demonstrated that administration of an MF59-adjuvanted vaccine formulation elicited a strong immune response with good safety. The levels of neutralizing antibodies induced were comparable to those observed in COVI D-19 patients, with 75 % of the participants achieving neutralizing antibody titers higher than those found in convalescent individuals [84]. In addition, a 2019 clinical trial assessing the safety and immunogenicity of a recombinant respiratory syncytial virus (RSV) protein vaccine in healthy adults showed that the MF59-adjuvanted formulation induced a 4.55-fold increase in serum-binding antibody titers 28 days after the primary immunization compared to baseline levels, indicating that the vaccine was capable of eliciting a high-level immune response [85].

On the other hand, the AS01 adjuvant system, which combines liposomes with a TLR4 agonist, is capable of activating innate immune cells while also enhancing both humoral and cellular immune responses [86, 87], making it a focal point in the development of RSV vaccines. CpG1018, a TLR9 agonist, can induce a Th1-type immune response and enhance protection against viral infections [66,88].While these classical adjuvants each play vital roles, their singular mechanisms can sometimes fall short in eliciting highly effective immune responses against ever-evolving pathogens. Additionally, AS03 is a water-in-oil emulsion primarily used in influenza vaccines. Two AS03-adjuvanted H5N1 influenza vaccines, Prepandrix and Q-Pan H5N1, have been approved for market use. Compared with non-adjuvanted vaccines, AS03-H1N1 influenza virus vaccines induce stronger humoral immune responses [89]. The inclusion of AS03 in H5N1 influenza vaccines reduces the required antigen dose while inducing more robust T cell and B cell responses [90]. AS03 has also been applied in the development of SARS-CoV-2 vaccines. Results from a Phase II clinical trial of the AS03-adjuvanted SARS-CoV-2 recombinant protein vaccine,CoV2 preSdTM demonstrated that the seropositivity rate for neutralizing antibodies after the second dose was 95 %–100 % in healthy adults, regardless of prior SARS-CoV-2 infection status. A Phase III clinical trial is currently underway to further evaluate the vaccine's immunogenicity [91].

To further enhance the immunogenicity of protein-based vaccines, in addition to adjuvants already approved or widely used such as MF59, AS01, AS03, and CpG1018, novel or investigational adjuvants—including STING agonists, ISCOMs, MA103, TLR agonists, Advax, and Poly(I:C)—are currently undergoing systematic evaluation. STING agonists activate intracellular signaling pathways, promoting the secretion of inflammatory and cytokine factors, thereby strengthening adaptive immune responses. ISCOMs,composed of saponins and phospholipids, are capable of stimulating both humoral and cellular immunity.Compared with aluminum-based adjuvants, mice immunized with a SARS-CoV-2 recombinant protein vaccine formulated with ISCOMs showed significantly higher levels of neutralizing antibodies upon ex vivo stimulation of splenic mononuclear cells [92]. In another study, mice were intranasally immunized with a fusion protein antigen composed of influenza virus nucleoprotein and membrane protein combined with ISCOMs, and subsequently challenged with H3N2 virus. The mice showed a 100 % survival rate, and exhibited higher levels of cytokine secretion from splenic cells, as well as increased levels of antigen-specific IgA and IgG in the local mucosa, indicating a strong mucosal immune response [93]. MA103 is a novel water-soluble adjuvant. In a study of a SARS-CoV-2 recombinant protein vaccine, formulations containing MA103 induced significantly higher titers of neutralizing antibodies in mice compared to those containing aluminum hydroxide or MF59, with antibody levels comparable to those induced by Moderna's mRNA-1273 vaccine [94]. Another animal study on a human RSV vaccine demonstrated that MA103-based formulations significantly enhanced Th1-type immune responses. Following viral challenge, mice exhibited markedly reduced RSV titers in the lungs, suggesting that MA103-containing formulations can lower pulmonary viral loads and alleviate histopathological damage in lung tissue [95, 96].

In addition to adjuvants such as MF59, AS01, AS03, and CpG1018, an increasing number of adjuvants have been applied in clinical studies of vaccines against respiratory infectious diseases such as SARS-CoV-2, influenza, and RSV. For instance, Toll-like receptor (TLR) agonists are used to enhance vaccine-induced Th1-type immune responses. Among them, TLR7/8 agonists (such as imiquimod) have shown potential to enhance cellular immunity in RSV subunit vaccines [97]. In SARS-CoV-2 vaccines, adjuvants like Advax™—a polysaccharide particle based on delta inulin—have significantly increased neutralizing antibody titers and T cell responses in animal models of RBD protein vaccines, while demonstrating good safety profiles. Advax™ has now entered clinical trial stages [98], Another example is Poly(I:C), a synthetic analog of double-stranded RNA, which has been used as an adjuvant in influenza and coronavirus vaccines. It mimics viral infection to activate dendritic cells and enhance immunogenicity [99]. Moreover, novel nanoparticle-based delivery systems such as lipid nanoparticles (LNPs) and polymeric nanoparticles (e.g.,PLGA) are increasingly being used in conjunction with adjuvants to improve antigen stability and transmembrane transport efficiency [100–102]. In the field of RSV vaccines, adjuvant combination strategies are also being explored—for example, the co-administration of TLR4 agonists with cationic liposomes to enhance mucosal immune responses [97]. These novel adjuvants and delivery systems not only enhance the quality of immune responses induced by vaccines but also show great potential in extending immune durability, reducing antigen dosage, and minimizing side effects.Preclinical and early-phase clinical studies have demonstrated that the combination of these adjuvants with structurally optimized antigens and nanoparticle platforms can significantly improve vaccine efficacy across different populations.

Adjuvants are a critical component of vaccine development. Currently, adjuvants with single functions are no longer sufficient to meet the demands of next-generation vaccine development. The future direction of vaccine adjuvant research will focus on improving immunogenicity and protective efficacy through personalized design and the application of novel adjuvant technologies, to better address the threat of infectious diseases. These innovations are expected to bring new breakthroughs in vaccine development and application, providing more effective tools for the prevention and control of infectious diseases. In summary, investigating the characteristics and mechanisms of different adjuvants is conducive to developing novel combined adjuvants by integrating different types, which holds great potential in the development of next-generation vaccines.(Table 2)

4. Challenges and future directions

4.1. Immunological durability and broad-spectrum protection

In the development of protein vaccines, although their safety and mild immune responses have been widely recognized, there are still shortcomings in terms of immunological durability and broad-spectrum protection. Existing data indicate that the protective efficacy of mRNA vaccines significantly declines within six months after administration, whereas some protein vaccines, such as the Novavax product, are able to maintain high levels of neutralizing antibodies even eight months post-vaccination [14], This observation suggests that through optimization of antigen design and delivery systems, protein vaccines have the potential

Table 2
Adjuvant features and components.

Adjuvant	Classification	Components	Proposed mode of action	Component of (licensed vaccines)	Immune effect
Alum	Aluminum Hydroxide	$Al(OH)_3$	Forms antigen depot, activates APCs via inflammasome pathways.	Hepatitis B vaccine (Engerix-B), HPV vaccine (Cervarix), DTaP/Tdap vaccines.	Primarily induces Th2-type humoral immunity: high titers of IgG1/IgE antibodies, but weaker Th1 and CD8 + T cell responses [110].
AS04	Combination(Alum + TLR4 agonist)	Aluminum salt + MPL	TLR4 activation + sustained antigen exposure.	Used in Cervarix®.	Induces Th1/Th2 balanced immunity [111].
MF59	Emulsion (Oil-in-water)	Squalene, Tween80, Span 85	Recruits APCs, enhances antigen uptake.	Fluad® (influenza vaccine).	Enhances antibody titers, particularly effective in elderly populations [110].
AS03	Emulsion (Oil-in-water)	Squalene, Vitamin E, Polysorbate80	Enhances innate immunity and cytokine response.	Pandemrix®, Q-Pan H5N1 (H1N1 and H5N1 influenza vaccines).	Enhances Th1/Th2 responses and cross-protection [112].
LNPs (Lipid Nanoparticles)	Delivery system + innate immune stimulator	Ionizable lipids, PEG-lipids, cholesterol, helper lipids	Protects mRNA and delivers it into cells; also acts as an innate immune activator (via inflammasome, TLR pathways).	Pfizer-BioNTech (BNT162b2) and Moderna (mRNA−1273) COVID−19 vaccines.	Enhances antigen expression and innate immune priming [113].
AS01	Liposome-based combination	Liposomes + MPL + QS−21	Promotes strong Th1 CD4 + T cell and antibody responses	Shingrix® (herpes zoster vaccine), Mosquirix® (malaria vaccine), RSV PreF vaccine candidates.	Enhances CD4 + T cell and antibody responses [111].
Matrix-M	Saponin-based nanoparticle	Saponins, cholesterol, phospholipids.	Activates APCs, enhances Th1/Th2 and CTL responses	Novavax® COVID−19 vaccine (NVX-CoV2373).	Boosts neutralizing antibody and T cell responses [114].
CpG1018	TLR9 agonist	Synthetic CpG oligonucleotides	Activates DCs, induces Th1-biased immunity	HEPLISAV-B® (hepatitis B vaccine).	Improves seroconversion rates and reduces dose requirements [115].
STING agonists	Cytosolic DNA sensor pathway activator	Cyclic dinucleotides.	Stimulates type I IFN via STING pathway	Under investigation for cancer immunotherapy and infectious disease vaccines.	Shows enhanced immunogenicity in preclinical trials [116].
ISCOMs	Immunostimulating Complexes	Saponins, cholesterol, phospholipids.	Enhances cross-presentation and CTL responses	Used in veterinary vaccines; under evaluation for human influenza and COVID−19 vaccines.	Strong mucosal and systemic immune responses [114].
MA103	Novel polymer-based aqueous adjuvant	Water-soluble polymers	Enhances Th1/Th2 response and antigen persistence	Preclinical studies for COVID−19 and RSV vaccines	Induces high neutralizing antibody titers and strong Th1 responses [117].

to further extend the duration of immune protection [103]. In the future, multivalent antigen design technologies are expected to integrate conserved antigens from different viral variants into a single vaccine formulation, thereby inducing a more comprehensive and long-lasting cross-immune response [104]. At the same time, using nanoparticle platforms for antigen presentation can not only enhance the stability of antigens but also improve B cell activation through multivalent display, leading to the formation of more robust immune memory [105]. Such strategies will contribute to improving the broad-spectrum protective capacity of vaccines against emerging variants and provide a solid foundation for the long-term prevention and control of infectious diseases.

4.2. Large-scale production and accessibility

Although protein vaccines have certain advantages in large-scale production and distribution, they still face challenges such as high production costs and long processing times. Currently, insect cell expression systems can improve antigen yields to some extent, but this system still requires further optimization in terms of protein purification and quality control to reduce production costs. Meanwhile, the storage and transportation of vaccines cannot be overlooked. Although protein vaccines are generally stable at 2–8°C, ensuring the effective operation of the cold chain logistics during global distribution, especially in remote and resource-limited areas, remains a pressing challenge. Only by achieving breakthroughs in production processes, cost control, and logistics support can protein vaccines become more competitive and accessible for large-scale application.

Future research will focus on the synergistic optimization of multiple aspects. First, in antigen design, in-depth analysis of the virus's high-resolution structure to develop more stable and immunogenic antigen variants will be key to enhancing the long-term protective effects of vaccines. Secondly, the continuous development of novel nanoparticle platforms and adjuvant combinations will provide more efficient antigen delivery and immune-enhancing solutions for protein vaccines, promoting broader and more durable immune memory.

On this basis, artificial intelligence (AI) is poised to exert an even more profound impact on antigen design, rather than being limited to process optimization or manufacturing. Leveraging deep learning, generative models and graph-based neural networks, researchers can mine large-scale viral genomic, antigen–antibody complex and immunological databases to identify conserved epitopes, predict their three-dimensional conformations and immunogenicity, and rapidly generate candidate antigen sequences. In particular, for highly mutable respiratory pathogens such as SARS-CoV-2, influenza virus and RSV, AI can track antigenic drift in real time, facilitate the design of cross-protective multivalent or mosaic antigens, and perform in-silico simulations of B- and T-cell responses to pre-screen candidates, thereby markedly shortening experimental timelines and reducing development costs. As tools such as AlphaFold are increasingly integrated with immune-simulation and molecular-docking platforms, AI is expected to enable end-to-end intelligent prediction and optimization of the "antigen sequence--structure–immune response" continuum, driving next-generation protein vaccines toward enhanced stability, breadth and durability, and providing stronger technological support for the control of respiratory infectious diseases.

In summary, through the comprehensive application of structural biology, nanotechnology, immunology, advanced production processes, and artificial intelligence (AI), future protein vaccines are expected to play a greater role in the prevention and control of respiratory infectious diseases, providing stronger protection for global public health safety.

5. Conclusion and outlook

Protein vaccines designed through structural approaches offer a promising and rational strategy for the prevention and control of respiratory infectious diseases. With advances in structural biology, immunology, and nanotechnology, antigen optimization strategies have been continuously refined, enabling protein vaccines to better mimic the native conformation of pathogens and thereby improve immunogenic recognition and immune activation. When integrated with nanoparticle-based delivery systems, these vaccines demonstrate enhanced structural stability and immunological efficacy. Moreover, the application of novel adjuvants significantly improves immune durability and broad-spectrum protection (Fig. 2). These innovations highlight the substantial potential of protein vaccines in combating respiratory pathogens such as SARS-CoV-2, influenza, and RSV—offering not only targeted protection against individual viruses but also enabling cross-protection against emerging variants through multivalent antigen designs and engineered delivery platforms.

Despite their favorable immunogenic and safety profiles, protein vaccines still face challenges regarding immune durability, manufacturing scalability, and global applicability. Although certain formulations sustain high levels of neutralizing antibodies post-vaccination, their duration of protection remains suboptimal and requires improvement—particularly for rapidly evolving viruses where frequent booster doses are impractical. While structural design targeting conserved antigenic regions has enhanced cross-protective potential, ensuring effectiveness against future variants necessitates continued investigation. Additionally, although protein vaccines offer logistical advantages over mRNA platforms in storage and transport, their relatively long production cycles and high costs remain obstacles. Improving production yield, lowering costs, and expanding manufacturing capacity will be critical to the feasibility of global implementation.

Looking ahead, future research should prioritize the continued refinement of vaccine formulations to enhance immunogenicity, durability, and cross-strain efficacy. Understanding viral immune escape mechanisms will be essential to ensure vaccines retain efficacy in the face of viral evolution. Meanwhile, the development of personalized immunization strategies is anticipated to become a key focus of future research. By integrating precision medicine approaches—such as host immune profiling and genomic analysis—vaccines can be tailored to individual immunological needs, thereby maximizing their effectiveness. In this context, artificial intelligence (AI) is emerging as a transformative force in vaccine research and production. AI technologies are increasingly being used to predict antigen structures, identify immunogenic epitopes, and analyze multidimensional immunological data during preclinical and clinical studies. Moreover, AI can model and optimize production parameters, improving yield and quality control while minimizing resource consumption. At the public health level, AI applications extend to epidemic modeling, vaccination planning, and logistical optimization, significantly enhancing vaccine accessibility and distribution. In the coming era, the integration of AI with structural biology, immunology, and materials science is expected to accelerate the intelligent design, precision manufacturing, and global deployment of next-generation protein vaccines, enabling a transition from empirical to data-driven paradigms in vaccine development.

Author statement

The authors declare that there are no conflicts of interest related to this manuscript.

CRediT authorship contribution statement

Ruiqi Weng: Writing – review & editing. **Yanjun Zhang:** Writing – review & editing. **Jianhua Li:** Writing – review & editing. **Keda Chen:** Writing – review & editing, Funding acquisition. **Tie xiaotian:** Writing – review & editing, Data curation. **Jiaxuan Li:** Writing – review & editing. **Hao Wu:** Writing – review & editing.

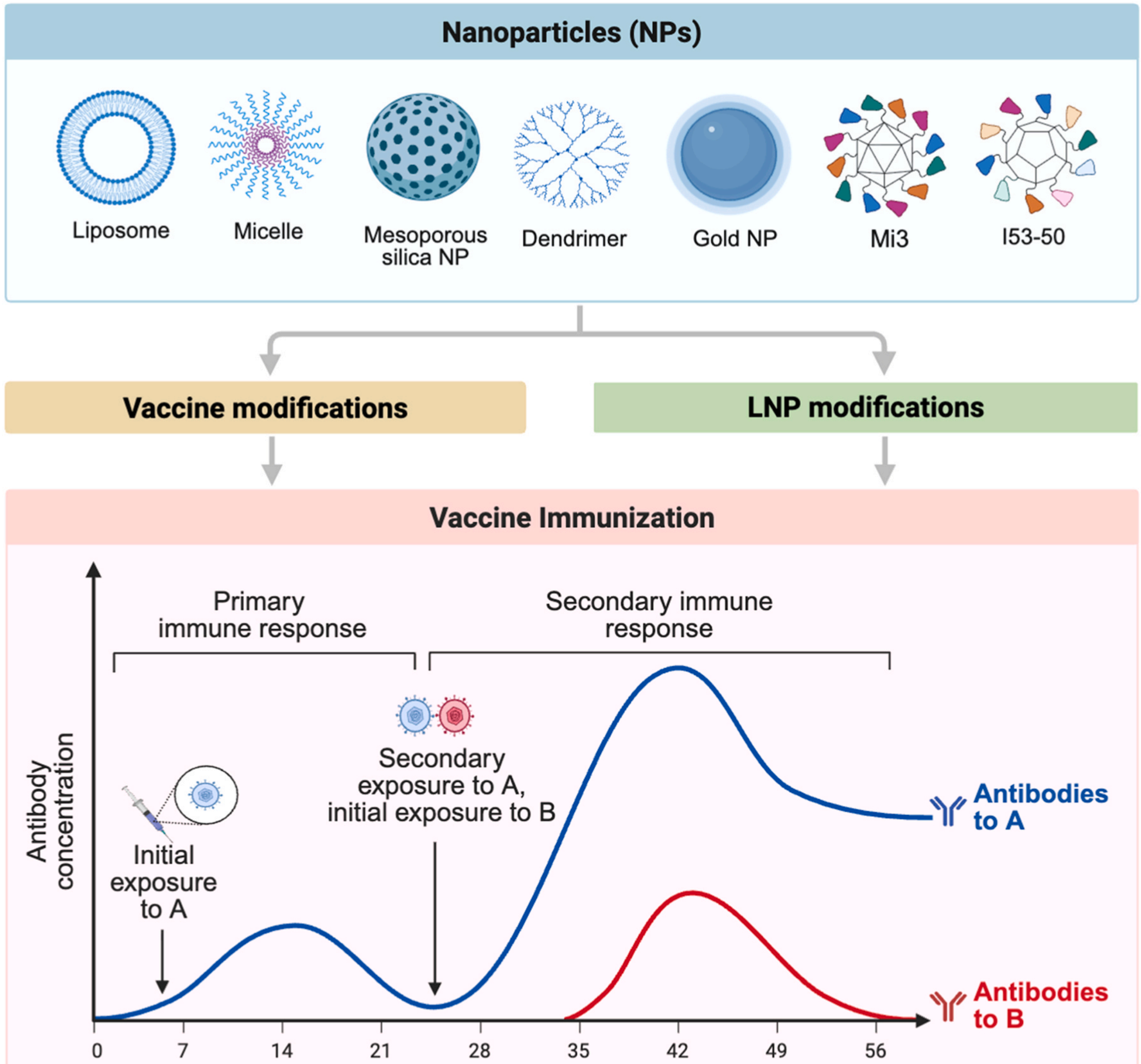

Fig. 2. Summary of nanoparticle modifications and their role in vaccine immunization.Illustrates various types of nanoparticles (such as liposomes, micelles, gold nanoparticles, etc.) and their applications in vaccine modifications, with a focus on their impact on immune responses. The graph also shows antibody concentration changes during primary and secondary immune responses, emphasizing the importance of nanoparticle and lipid nanoparticle (LNP) modifications in enhancing immune responses.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

This study was funded by the Provincial Industry-University Cooperation Collaborative Education Project (NO.318 [2022] of the Zhejiang Development Reform Society) and the University Level Scientific Research Project of Zhejiang Shuren University (Grant No: 2024R057), Natural Science Foundation of China, Grant/Award Number: 82151220; the National Natural Science Foundation of China (projects number U20A20410).

Declaration of Competing Interest

All other authors declare they have no competing interests.

Acknowledgements

Authors thank all the researchers, doctors, nurses, medical technicians, front-line workers, and public health officials for their hard work during this pandemic.

Data availability

Not applicable.

References

[1] Zuo L, Liu Q, Zhang K, Zhao L, Lin S, Dai Y, et al. Self-amplifying mRNA vaccines protect elderly BALB/c mice against a lethal respiratory syncytial virus infection. Mol Ther 2025;33(2):499–513.
[2] Hagman K, Postigo T, Diez-Castro D, Ursing J, Bermejo-Martin JF, de la Fuente A, et al. Prevalence and clinical relevance of viraemia in viral respiratory tract infections: a systematic review. Lancet Microbe 2025;6(2):100967.
[3] Montgomery MP, Morris SE, Rolfes MA, Kittikraisak W, Samuels AM, Biggerstaff M, et al. The role of asymptomatic infections in influenza transmission: what do we really know. Lancet Infect Dis 2024;24(6):e394–404.
[4] Lamers MM, Beumer J, van der Vaart J, Knoops K, Puschhof J, Breugem TI, et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020;369 (6499):50–4.

[5] Adeleke RA, Sahler J, Choi A, Roth K, Upadhye V, Ezzatpour S, et al. Replication-incompetent VSV-based vaccine elicits protective responses against SARS-CoV-2 and influenza virus. Sci Adv 2025;11(5):eadq4545.
[6] Wang Z, Li Z, Shi W, Zhu D, Hu S, Dinh PC, et al. A SARS-CoV-2 and influenza double hit vaccine based on RBD-conjugated inactivated influenza a virus. Sci Adv 2023;9(25):eabo4100.
[7] He X, Chen X, Wang H, Du G, Sun X. Recent advances in respiratory immunization: a focus on COVID-19 vaccines. J Control Release 2023;355:655–74.
[8] Li Q, Li H, Li Z, Wang Y. Vaccine and therapeutic agents against the respiratory syncytial virus: resolved and unresolved issue. MedComm (2020) 2024;5(12):e70016.
[9] Mazur NI, Terstappen J, Baral R, Bardají A, Beutels P, Buchholz UJ, et al. Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape. Lancet Infect Dis 2023;23(1):e2–21.
[10] Chow MYT, Pan HW, Seow HC, Lam JKW. Inhalable neutralizing antibodies - promising approach to combating respiratory viral infections. Trends Pharm Sci 2023;44(2):85–97.
[11] Wang Y, Wang D, Zhang L, Sun W, Zhang Z, Chen W, et al. Intra-host variation and evolutionary dynamics of SARS-CoV-2 populations in COVID-19 patients. Genome Med 2021;13(1):30.
[12] Lei H, Alu A, Yang J, He C, Shi J, Hong W, et al. Intranasal inoculation of cationic crosslinked carbon Dots-Adjuvanted respiratory syncytial virus f subunit vaccine elicits mucosal and systemic humoral and cellular immunity. MedComm (2020) 2025;6(4):e70146.
[13] Hotez PJ, Bottazzi ME. Whole inactivated virus and Protein-Based COVID-19 vaccines. Annu Rev Med 2022;73:55–64.
[14] Feng Q, Cheng K, Zhang L, Wang D, Gao X, Liang J, et al. Rationally designed multimeric nanovaccines using icosahedral DNA origami for display of SARS-CoV-2 receptor binding domain. Nat Commun 2024;15(1):9581.
[15] Tao P, Kuang Y, Li Y, Li W, Gao Z, Liu L, et al. Selection of a full agonist combinatorial antibody that rescues leptin deficiency in vivo. Adv Sci 2020;7(16):2000818.
[16] Miwa H, Antao OQ, Kelly-Scumpia KM, Baghdasarian S, Mayer DP, Shang L, et al. Improved humoral immunity and protection against influenza virus infection with a 3d porous biomaterial vaccine. Adv Sci (Weinh) 2023;10(31):e2302248.
[17] Vishweshwaraiah YL, Dokholyan NV. Toward rational vaccine engineering. Adv Drug Deliv Rev 2022;183:114142.
[18] Alameh MG, Tombácz I, Bettini E, Lederer K, Sittplangkoon C, Wilmore JR, et al. Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust t follicular helper cell and humoral responses. Immunity 2021;54(12):2877–92. e7.
[19] Jiang Y, Lei L, Zhao M, Tian Y, Huang Y, Yang M. Nanocarrier vaccines for respiratory infections. Trends Mol Med 2025.
[20] Leekha A, Saeedi A, Kumar M, Sefat K, Martinez-Paniagua M, Meng H, et al. An intranasal nanoparticle STING agonist protects against respiratory viruses in animal models. Nat Commun 2024;15(1):6053.
[21] Huang WC, Zhou S, He X, Chiem K, Mabrouk MT, Nissly RH, et al. SARS-CoV-2 RBD neutralizing antibody induction is enhanced by particulate vaccination. Adv Mater 2020;32(50):e2005637.
[22] Pallesen J, Wang N, Corbett KS, Wrapp D, Kirchdoerfer RN, Turner HL, et al. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci USA 2017;114(35):E7348–e57.
[23] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367(6483):1260–3.
[24] McLellan JS, Chen M, Leung S, Graepel KW, Du X, Yang Y, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. Science 2013;340(6136):1113–7.
[25] Krarup A, Truan D, Furmanova-Hollenstein P, Bogaert L, Bouchier P, Bisschop IJM, et al. A highly stable prefusion RSV f vaccine derived from structural analysis of the fusion mechanism. Nat Commun 2015;6:8143.
[26] Yassine HM, Boyington JC, McTamney PM, Wei CJ, Kanekiyo M, Kong WP, et al. Hemagglutinin-stem nanoparticles generate heterosubtypic influenza protection. Nat Med 2015;21(9):1065–70.
[27] Kanekiyo M, Joyce MG, Gillespie RA, Gallagher JR, Andrews SF, Yassine HM, et al. Mosaic nanoparticle display of diverse influenza virus hemagglutinins elicits broad b cell responses. Nat Immunol 2019;20(3):362–72.
[28] Oladejo M, Tijani AO, Puri A, Chablani L. Adjuvants in cutaneous vaccination: a comprehensive analysis. J Control Release 2024;369:475–92.
[29] Kim MY, Mason HS, Ma JKC, Reljic R. Recombinant immune complexes as vaccines against infectious diseases. Trends Biotechnol 2024;42(11):1427–38.
[30] Sagawa ZK, Goman C, Frevol A, Blazevic A, Tennant J, Fisher B, et al. Safety and immunogenicity of a thermostable ID93 + GLA-SE tuberculosis vaccine candidate in healthy adults. Nat Commun 2023;14(1):1138.
[31] Teplensky MH, Dittmar JW, Qin L, Wang S, Evangelopoulos M, Zhang B, et al. Spherical nucleic acid vaccine structure markedly influences adaptive immune responses of clinically utilized prostate cancer targets. Adv Health Mater 2021;10(22):e2101262.
[32] Wei X, Decker JM, Wang S, Hui H, Kappes JC, Wu X, et al. Antibody neutralization and escape by HIV-1. Nature 2003;422(6929):307–12.
[33] Hsieh CL, Goldsmith JA, Schaub JM, DiVenere AM, Kuo HC, Javanmardi K, et al. Structure-based design of prefusion-stabilized SARS-CoV-2 spikes. Science 2020;369(6510):1501–5.
[34] Hsieh CL, Rush SA, Palomo C, Chou CW, Pickens W, Más V, et al. Structure-based design of prefusion-stabilized human metapneumovirus fusion proteins. Nat Commun 2022;13(1):1299.
[35] Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med 2020;383(20):1920–31.
[36] McLellan JS, Chen M, Joyce MG, Sastry M, Stewart-Jones GB, Yang Y, et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. Science 2013;342(6158):592–8.
[37] Nachbagauer R, Feser J, Naficy A, Bernstein DI, Guptill J, Walter EB, et al. A chimeric hemagglutinin-based universal influenza virus vaccine approach induces broad and long-lasting immunity in a randomized, placebo-controlled phase I trial. Nat Med 2021;27(1):106–14.
[38] Yang S, Li Y, Dai L, Wang J, He P, Li C, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis 2021;21(8):1107–19.
[39] Swanson KA, Rainho-Tomko JN, Williams ZP, Lanza L, Peredelchuk M, Kishko M, et al. A respiratory syncytial virus (RSV) f protein nanoparticle vaccine focuses antibody responses to a conserved neutralization domain. Sci Immunol 2020;5(47).
[40] Gidwani SV, Brahmbhatt D, Zomback A, Bassie M, Martinez J, Zhuang J, et al. Engineered dityrosine-bonding of the RSV prefusion f protein imparts stability and potency advantages. Nat Commun 2024;15(1):2202.
[41] Ueda G, Antanasijevic A, Fallas JA, Sheffler W, Copps J, Ellis D, et al. Tailored design of protein nanoparticle scaffolds for multivalent presentation of viral glycoprotein antigens. Elife 2020;9.
[42] Walls AC, Miranda MC, Pham MN, Schäfer A, Greaney A, Arunachalam PS, et al. Elicitation of broadly protective sarbecovirus immunity by receptor-binding domain nanoparticle vaccines. bioRxiv 2021.
[43] Zhang X, Wu S, Liu J, Chen R, Zhang Y, Lin Y, et al. A mosaic nanoparticle vaccine elicits potent mucosal immune response with significant Cross-Protection activity against multiple SARS-CoV-2 sublineages. Adv Sci 2023;10(27):e2301034.
[44] Kelly HG, Tan HX, Juno JA, Esterbauer R, Ju Y, Jiang W, et al. Self-assembling influenza nanoparticle vaccines drive extended germinal center activity and memory b cell maturation. JCI Insight 2020;5(10).
[45] Tang P, Cui E, Cheng J, Li B, Tao J, Shi Y, et al. A ferritin nanoparticle vaccine based on the hemagglutinin extracellular domain of swine influenza a (H1N1) virus elicits protective immune responses in mice and pigs. Front Immunol 2024;15:1361323.
[46] Qiao Y, Li S, Jin S, Pan Y, Shi Y, Kong W, et al. A self-assembling nanoparticle vaccine targeting the conserved epitope of influenza virus hemagglutinin stem elicits a cross-protective immune response. Nanoscale 2022;14(8):3250–60.
[47] Chen T, Gao Y, Chen X, Dong Y, Wang S, Huang Q, et al. Self-assembling nanoparticle vaccine elicits a robust protective immune response against avian influenza H5N6 virus in chickens. Int J Biol Macromol 2025;287:138405.
[48] Nie J, Wang Q, Li C, Zhou Y, Yao X, Xu L, et al. Self-Assembled multiepitope nanovaccine provides Long-Lasting Cross-Protection against influenza virus. Adv Health Mater 2024;13(10):e2303531.
[49] Wang Z, Zhang B, Ou L, Qiu Q, Wang L, Bylund T, et al. Extraordinary titer and broad Anti-SARS-CoV-2 neutralization induced by stabilized RBD nanoparticles from strain BA.5. Vaccines 2023;12(1).
[50] Kanekiyo M, Wei CJ, Yassine HM, McTamney PM, Boyington JC, Whittle JR, et al. Self-assembling influenza nanoparticle vaccines elicit broadly neutralizing H1N1 antibodies. Nature 2013;499(7456):102–6.
[51] Song G, Yuan M, Liu H, Capozzola T, Lin RN, Torres JL, et al. Broadly neutralizing antibodies targeting a conserved silent face of spike RBD resist extreme SARS-CoV-2 antigenic drift. Cell Rep 2025;44(7):115948.
[52] Yang Z, Hua L, Yang M, Li W, Ren Z, Zheng X, et al. Polymerized porin as a novel delivery platform for coronavirus vaccine. J Nanobiotechnol 2022;20(1):260.
[53] Yu F, Xiang R, Deng X, Wang L, Yu Z, Tian S, et al. Receptor-binding domain-specific human neutralizing monoclonal antibodies against SARS-CoV and SARS-CoV-2. Signal Transduct Target Ther 2020;5(1):212.
[54] Dangi T, Palacio N, Sanchez S, Park M, Class J, Visvabharathy L, et al. Cross-protective immunity following coronavirus vaccination and coronavirus infection. J Clin Invest 2021;131(24).
[55] Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 2020;586(7830):583–8.
[56] Rodrigues MQ, Alves PM, Roldão A. Functionalizing ferritin nanoparticles for vaccine development. Pharmaceutics 2021;13(10).
[57] Cho KJ, Shin HJ, Lee JH, Kim KJ, Park SS, Lee Y, et al. The crystal structure of ferritin from helicobacter pylori reveals unusual conformational changes for iron uptake. J Mol Biol 2009;390(1):83–98.
[58] Fu D, Wang W, Zhang Y, Zhang F, Yang P, Yang C, et al. Self-assembling nanoparticle engineered from the ferritinophagy complex as a rabies virus vaccine candidate. Nat Commun 2024;15(1):8601.
[59] Georgiev IS, Joyce MG, Chen RE, Leung K, McKee K, Druz A, et al. Two-Component ferritin nanoparticles for multimerization of diverse trimeric antigens. ACS Infect Dis 2018;4(5):788–96.
[60] Ma X, Zou F, Yu F, Li R, Yuan Y, Zhang Y, et al. Nanoparticle vaccines based on the receptor binding domain (RBD) and heptad repeat (HR) of SARS-CoV-2 elicit robust protective immune responses. Immunity 2020;53(6). 1315-30.e9.
[61] Johnston SC, Ricks KM, Lakhal-Naouar I, Jay A, Subra C, Raymond JL, et al. A SARS-CoV-2 spike ferritin nanoparticle vaccine is protective and promotes a

strong immunological response in the cynomolgus macaque coronavirus disease 2019 (COVID-19) model. Vaccines 2022;10(5).
[62] Houser KV, Chen GL, Carter C, Crank MC, Nguyen TA, Burgos Florez MC, et al. Safety and immunogenicity of a ferritin nanoparticle H2 influenza vaccine in healthy adults: a phase 1 trial. Nat Med 2022;28(2):383–91.
[63] Bergeron HC, Murray J, Juarez MG, Nangle SJ, DuBois RM, Tripp RA. Immunogenicity and protective efficacy of an RSV g S177Q central conserved domain nanoparticle vaccine. Front Immunol 2023;14:1215323.
[64] Bale JB, Gonen S, Liu Y, Sheffler W, Ellis D, Thomas C, et al. Accurate design of megadalton-scale two-component icosahedral protein complexes. Science 2016; 353(6297):389–94.
[65] Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, et al. Distinct antibody and memory b cell responses in SARS-CoV-2 naive and recovered individuals following mRNA vaccination. Sci Immunol 2021;6(58).
[66] Arunachalam PS, Walls AC, Golden N, Atyeo C, Fischinger S, Li C, et al. Adjuvanting a subunit COVID-19 vaccine to induce protective immunity. Nature 2021;594(7862):253–8.
[67] He L, Lin X, Wang Y, Abraham C, Sou C, Ngo T, et al. Single-component, self-assembling, protein nanoparticles presenting the receptor binding domain and stabilized spike as SARS-CoV-2 vaccine candidates. Sci Adv 2021;7(12).
[68] Kang YF, Sun C, Zhuang Z, Yuan RY, Zheng Q, Li JP, et al. Rapid development of SARS-CoV-2 spike protein Receptor-Binding domain Self-Assembled nanoparticle vaccine candidates. ACS Nano 2021;15(2):2738–52.
[69] Boyoglu-Barnum S, Ellis D, Gillespie RA, Hutchinson GB, Park YJ, Moin SM, et al. Quadrivalent influenza nanoparticle vaccines induce broad protection. Nature 2021;592(7855):623–8.
[70] Ren H, Zhang B, Zhang X, Wang T, Hou X, Lan X, et al. Self-Assembling nanoparticle hemagglutinin influenza vaccines induce high antibody response. Int J Mol Sci 2024;25(13).
[71] Vijayan A, Vogels R, Groppo R, Jin Y, Khan S, Van Kampen M, et al. A self-amplifying RNA RSV prefusion-F vaccine elicits potent immunity in pre-exposed and naive non-human primates. Nat Commun 2024;15(1):9884.
[72] Kanekiyo M, Bu W, Joyce MG, Meng G, Whittle JR, Baxa U, et al. Rational design of an Epstein-Barr virus vaccine targeting the Receptor-Binding site. Cell 2015; 162(5):1090–100.
[73] Marcandalli J, Fiala B, Ols S, Perotti M, de van der Schueren W, Snijder J, et al. Induction of potent neutralizing antibody responses by a designed protein nanoparticle vaccine for respiratory syncytial virus. Cell 2019;176(6):1420–31. e17.
[74] Kang YF, Sun C, Sun J, Xie C, Zhuang Z, Xu HQ, et al. Quadrivalent mosaic HexaPro-bearing nanoparticle vaccine protects against infection of SARS-CoV-2 variants. Nat Commun 2022;13(1):2674.
[75] Hutchinson GB, Abiona OM, Ziwawo CT, Werner AP, Ellis D, Tsybovsky Y, et al. Nanoparticle display of prefusion coronavirus spike elicits S1-focused cross-reactive antibody response against diverse coronavirus subgenera. Nat Commun 2023;14(1):6195.
[76] Braz Gomes K, Zhang YN, Lee YZ, Eldad M, Lim A, Ward G, et al. Single-Component multilayered Self-Assembling protein nanoparticles displaying extracellular domains of matrix protein 2 as a Pan-influenza a vaccine. ACS Nano 2023;17(23):23545–67.
[77] Pan J, Wang Q, Qi M, Chen J, Wu X, Zhang X, et al. An intranasal multivalent Epitope-Based nanoparticle vaccine confers broad protection against divergent influenza viruses. ACS Nano 2023;17(14):13474–87.
[78] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383 (27):2603–15.
[79] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5): 403–16.
[80] August A, Glenn GM, Kpamegan E, Hickman SP, Jani D, Lu H, et al. A phase 2 randomized, observer-blind, placebo-controlled, dose-ranging trial of aluminum-adjuvanted respiratory syncytial virus f particle vaccine formulations in healthy women of childbearing age. Vaccine 2017;35(30):3749–59.
[81] Zhang W, Cui H, Xu J, Shi M, Bian L, Cui L, et al. Biodistribution and mechanisms of action of MF59 and MF59-like adjuvants. J Control Release 2025;378:573–87.
[82] Huang S, Li Y, Zhang S, Chen Y, Su W, Sanchez DJ, et al. A self-assembled graphene oxide adjuvant induces both enhanced humoral and cellular immune responses in influenza vaccine. J Control Release 2024;365:716–28.
[83] Lederer K, Castano D, Gomez Atria D, Oguin TH, 3rd, Wang S, et al. SARS-CoV-2 mRNA vaccines foster potent Antigen-Specific germinal center responses associated with neutralizing antibody generation. Immunity 2020;53(6): 1281–95. e5.
[84] Chappell KJ, Mordant FL, Li Z, Wijesundara DK, Ellenberg P, Lackenby JA, et al. Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Infect Dis 2021;21(10):1383–94.
[85] Leroux-Roels G, De Boever F, Maes C, Nguyen TL, Baker S, Gonzalez Lopez A. Safety and immunogenicity of a respiratory syncytial virus fusion glycoprotein f subunit vaccine in healthy adults: results of a phase 1, randomized, observer-blind, controlled, dosage-escalation study. Vaccine 2019;37(20):2694–703.
[86] Bechtold V, Smolen KK, Burny W, de Angelis SP, Delandre S, Essaghir A, et al. Functional and epigenetic changes in monocytes from adults immunized with an AS01-adjuvanted vaccine. Sci Transl Med 2024;16(758):eadl3381.
[87] Lavelle EC, McEntee CP. Vaccine adjuvants: tailoring innate recognition to send the right message. Immunity 2024;57(4):772–89.
[88] Nanishi E, Borriello F, O'Meara TR, McGrath ME, Saito Y, Haupt RE, et al. An aluminum hydroxide:CpG adjuvant enhances protection elicited by a SARS-CoV-2 receptor binding domain vaccine in aged mice. Sci Transl Med 2022;14(629): eabj5305.
[89] Pillet S, Arunachalam PS, Andreani G, Golden N, Fontenot J, Aye PP, et al. Safety, immunogenicity, and protection provided by unadjuvanted and adjuvanted formulations of a recombinant plant-derived virus-like particle vaccine candidate for COVID-19 in nonhuman primates. Cell Mol Immunol 2022;19(2):222–33.
[90] Moris P, van der Most R, Leroux-Roels I, Clement F, Dramé M, Hanon E, et al. H5N1 influenza vaccine formulated with AS03 a induces strong cross-reactive and polyfunctional CD4 T-cell responses. J Clin Immunol 2011;31(3):443–54.
[91] Sridhar S, Joaquin A, Bonaparte MI, Bueso A, Chabanon AL, Chen A, et al. Safety and immunogenicity of an AS03-adjuvanted SARS-CoV-2 recombinant protein vaccine (CoV2 preS dTM) in healthy adults: interim findings from a phase 2, randomised, dose-finding, multicentre study. Lancet Infect Dis 2022;22(5): 636–48.
[92] Villarraza J, Fuselli A, Gugliotta A, Garay E, Rodríguez MC, Fontana D, et al. A COVID-19 vaccine candidate based on SARS-CoV-2 spike protein and immune-stimulating complexes. Appl Microbiol Biotechnol 2023;107(11):3429–41.
[93] Zhu W, Park J, Pho T, Wei L, Dong C, Kim J, et al. ISCOMs/MPLA-Adjuvanted SDAD protein nanoparticles induce improved mucosal immune responses and Cross-Protection in mice. Small 2023;19(34):e2301801.
[94] Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med 2020;383(16):1544–55.
[95] Terstappen J, Hak SF, Bhan A, Bogaert D, Bont LJ, Buchholz UJ, et al. The respiratory syncytial virus vaccine and monoclonal antibody landscape: the road to global access. Lancet Infect Dis 2024;24(12):e747–61.
[96] Song W, Song SJ, Kuang J, Yang H, Yu T, Yang F, et al. Activating innate immunity by a STING signal amplifier for local and systemic immunotherapy. ACS Nano 2022;16(10):15977–93.
[97] van Haren SD, Pedersen GK, Kumar A, Ruckwardt TJ, Moin S, Moore IN, et al. CAF08 adjuvant enables single dose protection against respiratory syncytial virus infection in murine newborns. Nat Commun 2022;13(1):4234.
[98] Rodrigues KA, Rodriguez-Aponte SA, Dalvie NC, Lee JH, Abraham W, Carnathan DG, et al. Phosphate-mediated coanchoring of RBD immunogens and molecular adjuvants to alum potentiates humoral immunity against SARS-CoV-2. Sci Adv 2021;7(50):eabj6538.
[99] Adams CS, Kim H, Burtner AE, Lee DS, Dobbins C, Criswell C, et al. De novo design of protein minibinder agonists of TLR3. Nat Commun 2025;16(1):1234.
[100] Jennewein MF, Schultz MD, Beaver S, Battisti P, Bakken J, Hanson D, et al. Intranasal replicon SARS-CoV-2 vaccine produces protective respiratory and systemic immunity and prevents viral transmission. Mol Ther 2025.
[101] Baldeon Vaca G, Meyer M, Cadete A, Hsiao CJ, Golding A, Jeon A, et al. Intranasal mRNA-LNP vaccination protects hamsters from SARS-CoV-2 infection. Sci Adv 2023;9(38):eadh1655.
[102] Forest V, Pourchez J. Nano-delivery to the lung - by inhalation or other routes and why nano when micro is largely sufficient? Adv Drug Deliv Rev 2022;183: 114173.
[103] Zhou H, Leng P, Wang Y, Yang K, Li C, Ojcius DM, et al. Development of t cell antigen-based human coronavirus vaccines against nAb-escaping SARS-CoV-2 variants. Sci Bull (Beijing) 2024;69(15):2456–70.
[104] Zhang J, Xu Y, Chen M, Wang S, Lin G, Huang Y, et al. Spatial engineering of heterotypic antigens on a DNA framework for the preparation of mosaic nanoparticle vaccines with enhanced immune activation against SARS-CoV-2 variants. Angew Chem Int Ed Engl 2024;63(46):e202412294.
[105] Gao X, Wang X, Li S, Saif Ur Rahman M, Xu S, Liu Y. Nanovaccines for advancing Long-Lasting immunity against infectious diseases. ACS Nano 2023;17(24): 24514–38.
[106] Kraft JC, Pham MN, Shehata L, Brinkkemper M, Boyoglu-Barnum S, Sprouse KR, et al. Antigen- and scaffold-specific antibody responses to protein nanoparticle immunogens. Cell Rep Med 2022;3(10):100780.
[107] He X, Zhang X, Wu B, Deng J, Zhang Y, Zhu A, et al. The receptor binding domain of SARS-CoV-2 omicron subvariants targets Siglec-9 to decrease its immunogenicity by preventing macrophage phagocytosis. Nat Immunol 2024;25 (4):622–32.
[108] Watanabe Y, Mendonca L, Allen ER, Howe A, Lee M, Allen JD, et al. Native-like SARS-CoV-2 spike glycoprotein expressed by ChAdOx1 nCoV-19/AZD1222 vaccine. ACS Cent Sci 2021;7(4):594–602.
[109] Nguyen TL, Yin Y, Choi Y, Jeong JH, Kim J. Enhanced cancer DNA vaccine via direct transfection to host dendritic cells recruited in injectable scaffolds. ACS Nano 2020;14(9):11623–36.
[110] Pulendran B, O'Hagan PSA. DT. Emerging concepts in the science of vaccine adjuvants. Nat Rev Drug Discov 2021;20(6):454–75.
[111] Ren H, Jia W, Xie Y, Yu M, Chen Y. Adjuvant physiochemistry and advanced nanotechnology for vaccine development. Chem Soc Rev 2023;52(15):5172–254.
[112] Reinke S, Pantazi E, Chappell GR, Sanchez-Martinez A, Guyon R, Fergusson JR, et al. Emulsion and liposome-based adjuvanted R21 vaccine formulations mediate protection against malaria through distinct immune mechanisms. Cell Rep Med 2023;4(11):101245.
[113] Li Z, Chen P, Qu A, Sun M, Xu L, Xu C, et al. Opportunities and challenges for nanomaterials as vaccine adjuvants. Small Methods 2025:e2402059.
[114] Zhao T, Cai Y, Jiang Y, He X, Wei Y, Yu Y, et al. Vaccine adjuvants: mechanisms and platforms. Signal Transduct Target Ther 2023;8(1):283.

[115] Qu Y, Ju Y, Cortez-Jugo C, Lin Z, Li S, Zhou J, et al. Template-Mediated assembly of DNA into microcapsules for immunological modulation. Small 2020;16(37):e2002750.
[116] Ding X, Sun M, Guo F, Qian X, Yuan H, Lou W, et al. Picrasidine s induces cGAS-Mediated cellular immune response as a novel vaccine adjuvant. Adv Sci 2024;11(32):e2310108.
[117] Ukidve A, Cu K, Goetz M, Angsantikul P, Curreri A, Tanner EEL, et al. Ionic-Liquid-Based safe adjuvants. Adv Mater 2020;32(46):e2002990.