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Review

Immunological Strategies for Enhancing Viral Neutralization and Protection in Antibody-Guided Vaccine Design

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Abstract

Background: Immunological strategies for antibody-guided vaccine design intend to enhance viral neutralization and protection and increase efficacy. Here, we discuss advances in antibody-guided vaccine design and current antibody-guided strategies, including epitope-based, nanoparticle-based, and scaffold-based vaccine approaches. We review the challenges and limitations of vaccines against different pathogens, such as influenza A virus, HIV-1 virus, single-celled malaria parasite, respiratory syncytial virus, and SARS-CoV-2. We summarize the available literature guidance, including emerging techniques in immunological vaccine design, to help understand and improve antibody-based immunity. The search strategy we applied is a comprehensive literature review of major databases, with specific search terms related to antibody-mediated vaccine design, viral neutralization, and immune protection. We discuss the how future directions for next-generation vaccine platforms and personalized vaccines based on immunogenetics will help improve vaccine design for increased specificity and potency of antibodies that neutralize pathogens, offering more precise and effective immune responses and, therefore, protection.

Keywords: antibody-guided vaccine; viral neutralization; immune protection; vaccine design; antibody-guided vaccine design; immune modulation; vaccine efficacy

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1. Introduction

Infectious diseases caused by viruses, bacteria, fungi, and parasites have been responsible for increasing mortality for decades [1,2]. The mechanisms for various types of infectious diseases still need to be fully understood. Still, vaccines have emerged as a common approach to their prevention [3].

In the past decade, the field of vaccine design has developed very fast. Different approaches are used to create them to induce effective protective immune responses. Over the years, many data have been accumulated in the literature about the immune system and the immune response. Vaccines are undoubtedly one of the greatest scientific achievements, having prevented the mortality and morbidity of millions of people from various deadly

diseases [4,5]. Various approaches have been tested, e.g., with whole organisms, killed, attenuated, and recombinant, and the goal has always been to protect and create an immune defense [6–9]. Recombinant DNA technology has helped develop subunit vaccines targeting individual antigens from pathogens [10,11]. This increases the safety profile, and the immunization directs the immune response only to the relevant target.

Isolation of human antibodies provides an innovative approach to identifying protective antigens that may form the basis of vaccine design [12]. This approach is still evolving, but significant progress has been made with vaccines against human immunodeficiency virus (HIV), influenza, respiratory syncytial virus (RSV), and others, and it has enormous potential to address many difficult disease targets successfully. When the immune system encounters an infectious agent, a polyclonal antibody response is generated against many proteins and non-protein antigens. Only some of these antibodies have a protective function. For example, in viral infection, a large number of antibodies are formed. Still, most lack neutralizing activity [12–15].

In recent years, neutralizing antibodies have been increasingly used to guide the design of viral vaccines. In vivo, neutralizing antibodies can help antiviral function, which are determined by in vitro assays. These assays also define the effector functions of antibodies to evaluate these antibodies against viruses and infected cells in effector systems. Interpretation of the results is difficult, but is important for choosing the most appropriate vaccine strategies.

Antibodies have various functions that determine an optimal immune response against viral particles. They are associated with neutralizing the virus and preventing viral spread, enhancing the host's endogenous antiviral immune response, and eliminating infected cells [16,17].

In general, neutralization assays involve a virus, an antibody, and a target cell. Cells bearing FcRs can directly or indirectly mediate the effector functions of antibodies. The elimination of infected cells occurs through various antibody effector mechanisms of antibodies such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and antibody-mediated complement-dependent cytotoxicity (CDC) [18]. In the ADCC mechanism, natural killer cells identify IgG-viral protein complexes in infected cells coated in nAbs via FcγR and and induce target cell death. In ADCP, effector cells that are coated with nAb virions bear a FcγR, may fail to bind to host cells and become sequestered or taken up by effector cells such as macrophages. In the CDC mechanism, binding of the C1q component of the complement, resulting in the opsonization of viruses or infected cells and leads to activation of the ADCP mechanism [19,20].

Antibodies may bind to the pathogen or complement factors, leading to complement-mediated lysis of viruses. They may also bind to complement receptors on immune cells, triggering the activation of these cells [21]. The role of opsonophagocytosis against foot-and-mouth disease (FMD) and malaria, and in the serological evaluation of pneumococcal vaccines, H. influenzae and S. Typhi, is known [22–25]. A very recent article describes the use of this mechanism to create a nanobody-based composite that recruits polyclonal immunoglobulins, attracts immune effectors, and kills cells infected with influenza virus [26].

Neutralizing antibodies are a marker of immunity against reinfection. There are vaccines that induce neutralizing antibodies lifelong [27–29]. Not all vaccines are like this; the reason is antigenic variability. In the case of influenza virus, antigens can change so frequently that influenza vaccines quickly become ineffective, leading to the development of a new vaccine each season [30,31]. Human immunodeficiency virus (HIV) is even more variable, and although most vaccines against it induce an immune response, this response is apparently insufficient for protection. The reason is that HIV disguises itself, so that even if we do make antibodies, the virus changes escape them [32].

Thus, the surface protein landscape and immunogenic characteristics offers the infectious agent the opportunity to limit the most effective response through a mechanism of antigenic competition. This approach can be applied to producing stable vaccine candidates that elicit highly specific antibody responses. However, the antigenic competition is more likely to occur with components of pathogens that are secreted or shed, rather than integral proteins of the virus. However, this notion is subject to debate, particularly in the context of highly immunogenic viral proteins, such as the hemagglutinin (HA) of influenza viruses and the spike proteins of coronaviruses. These proteins, despite their immunogenicity, undergo rapid mutations, which can compromise their effectiveness as vaccine targets. This highlights the need for further research to clarify the role of antigenic competition in immune responses and its implications for vaccine development.

In the last years of the COVID-19 pandemic, we have seen how new approaches, together with new technologies and methods, have generated new vaccines and given an appropriate immune response [15,33]. The efficacy of COVID-19 vaccines is largely attributed to their ability to present the spike protein, particularly the receptor-binding domain (RBD), to elicit neutralizing antibodies. However, recent studies have highlighted the significance of antibodies that target the N-terminal domain (NTD) of the spike protein. These antibodies provide an additional layer of neutralization by binding to conserved epitopes outside the RBD, interfering with viral entry and enhancing immune protection [34]. The inclusion of the NTD as a target in vaccine design offers potential advantages, such as broadening the immune response and improving efficacy against emerging variants with RBD mutations. Exploring the role of NTD-specific antibodies in neutralization and their incorporation into vaccine strategies aligns with the principles of antibody-guided vaccine design, which aims to leverage diverse epitopes to enhance immunogenicity and protection. Future vaccine platforms could benefit from further investigation of these non-RBD regions to ensure more comprehensive immune coverage [35].

In line with this, it is assumed that developing antibody-guided vaccines promises to provide an effective solution against infectious diseases by generating robust antibody responses while improving the safety profile. In this review, we aim to explore the factors and mechanisms related to viral immunity that can be used as strategies in antibody-guided vaccine design.

2. Search Strategy

We conducted a comprehensive literature review using multiple databases (including Scopus, PubMed, and MEDLINE). The search used a combination of Medical Subject Headings (MeSHs) and free-text keywords to ensure a broad and inclusive retrieval of articles. The following search string was applied: (“antibody-guided vaccine” OR “antibody-mediated vaccine” OR “vaccine design”) AND (“viral neutralization” OR “immune protection” OR “antibody response”) AND (“immunological strategies” OR “immune modulation” OR “antibody-guided vaccine design”).

All relevant papers published until 1 November 2024, were considered, and studies were retrieved based on their title, abstract, and relevance. After the initial examination, duplicate articles were removed. The remaining papers were screened for eligibility, focusing on studies that discuss the chosen topic.

3. Background on Vaccine-Induced Immunity

Despite the great success of life-saving vaccines, they were developed empirically, with not a very good understanding of immunological mechanisms. Today, there is a large amount of scientific information about the immune system and different types of immune responses generating to protect against various pathogens.

Vaccines stimulate complex immune responses involving both innate and adaptive mechanisms. Protection is often mediated by pathogen-specific antibodies produced by plasma cells, a subset of terminally differentiated B lymphocytes. In addition to humoral immunity, cellular immunity plays a crucial role in vaccine efficacy by activating pathogen-specific T cells, including cytotoxic T lymphocytes that directly eliminate infected cells. Furthermore, helper T cells support B-cell activation and antibody production. A coordinated interplay between cellular and humoral immunity is essential for robust and durable protection against pathogens. After administration, vaccine antigens travel from the injection site to draining lymph nodes, where macrophages and other antigen-presenting cells capture and present them to B cells in follicles, triggering their activation and migration toward the marginal zone to interact with T cells [36]. Activated B cells can follow an extra-follicular pathway, producing short-lived plasma cells without T-cell assistance. This rapid response, often triggered by bacterial antigens like lipopolysaccharides, leads to low-affinity IgM antibody production and no isotype switching, providing only short-term protection [37]. The second pathway involves germinal center (GC) response induction, a slower but more coordinated process that begins in the lymph node's T-cell zone. Here, antigen-presenting cells present antigens to naive CD4+ T cells. This leads to helper T-cell (Th cell) differentiation, which supports B-cell activation and isotype switching to produce high-affinity IgG or IgE antibodies. Some T-cells differentiate into follicular helper T cells (TFH cells), maintaining the GC reaction and enabling long-term immune memory [38,39].

The mechanisms underpinning the durability of vaccine-induced immunity remain only partially understood, largely because many vaccines were developed empirically, without a full grasp of the immunological principles driving their long-term protection [40]. The durability of vaccine-induced immunity depends on factors like the pathogen's mutation rate (e.g., fast-mutating vs. stable viruses), the vaccine type (e.g., live-attenuated vs. inactivated, with or without adjuvants), and the vaccination schedule (dose number, interval, and timing). Understanding these variables is critical to improving long-term immune protection through vaccination [36]. Vaccines can provide different durations of protection. There are vaccines that provide long-lasting protection (>20 years), e.g., for measles, yellow fever, rubella, and hepatitis. Vaccines that provide a moderate duration of protection (about 5–20 years) are, e.g., polio vaccines, BCG vaccine, against mumps, and against herpes. A short duration of protection (<5 years) provides, e.g., the vaccines against Cholera, Rotavirus, and Influenza [41]. For example, vaccines against SARS-CoV-2 have proven highly effective in reducing the severity of the disease and providing significant protection against reinfection. However, in recent years, it has become clear that protection after vaccination or infection decreases over time. In addition, except for new variants of SARS-CoV-2 that evolve, some specific characteristics, such as age, comorbidities, ethnicity, and medication use, must be considered in order to assess the effectiveness of vaccines [42,43]. Evaluation of the efficacy and durability of immunity after vaccination has been performed in immunocompromised patients against SARS-CoV-2, influenza, and respiratory syncytial virus (RSV) [44]. The results showed different durability of immunity. In general, they showed similar waning of immunity defense over time and the need for booster doses. To sustain public trust in vaccines, it is necessary for new and adaptive strategies in vaccine design for more persistent and durable protection against rapidly mutating pathogens.

Like most drugs and substances, vaccines can sometimes cause specific reactions. These off-label benefits of vaccinations are called "para-specific effects" (PSEs) [45]. In a recent article, Arunachalam et al. discussed several secondary benefits of vaccination and novel mechanisms of para-specific protection by vaccination. These effects are non-specific and may prevent or worsen pre-existing host diseases (e.g., asthma, and cardiovascular

or autoimmune diseases) [46]. They proposed an "immuno-wave" model describing a vaccine-induced "Goldilocks immunity." Vaccines create a nuanced immune environment, balancing pro-inflammatory and anti-inflammatory responses from the innate and adaptive immune systems. This "quiet alert" immune state primes the body for rapid defense against pathogens while minimizing pathological inflammation or allergies [46].

Other vaccines with such effects are available. BCG vaccine reduces the likelihood of developing Alzheimer's disease [47], bladder cancer [48], diabetes type 1 [49], and chronic diseases [50]. A number of studies have shown that influenza vaccines provide protection against specific respiratory infections and cardiovascular diseases [51]. Studies have shown a protective PSE of influenza vaccination against severe COVID-19 [52]. There is even evidence about protection against SARS-CoV-2 infection after vaccination against measles, mumps, rubella, varicella, and hepatitis [53,54].

Most current vaccines induce protective immunity by stimulating antibodies that either block infection or prevent microbial invasion into the bloodstream. These antibodies must be functional, achieving protection through mechanisms like neutralization or opsonophagocytosis, as mentioned above. Protective correlates, often based on antibody levels, can vary and may be absolute or relative. For some diseases, there may be multiple correlates, including "co-correlates," involving both antibodies and cell-mediated immunity. When correlates of protection are uncertain or unmeasurable, surrogate markers, typically antibody levels, are used to predict vaccine efficacy [55]. The role of adaptive immunity has been well studied concerning vaccines and diseases, while innate immunity has received less attention. Although epigenetic changes in the innate immune system can lead to long-lasting "trained immunity," their direct and indirect effects on specific and unrelated infections remain underexplored [56].

4. Advances in Antibody-Guided Vaccine Design

The field of vaccine development has advanced significantly with the integration of antibody-guided vaccine design that elicits specific immune responses to effectively neutralize viral threats [57–59]. Here, we review current antibody-guided strategies, including structure/conformation-based, epitope-focused, nanoparticle-displayed, and scaffold-based vaccine approaches.

4.1. Rational Antigen Design Based on Structural Conformation of the Antigen and Epitopes

Modern vaccine strategies can produce stronger, longer-lasting immunity by focusing on antigen design and mimicking the key epitopes targeted by neutralizing antibodies [60]. Key immunological approaches in this area include rational antigen design, which seeks to shape antigens for optimal immune responses, and the mimicry of neutralizing antibody epitopes, guiding the immune system toward generating protective responses [61]. Corbett et al. explored these strategies, emphasizing how they contribute to more precise and resilient vaccines [62]. During the process of antibody-guided vaccine development, it is crucial to rationally design the antigen. Constructed antigens should trigger strong, specific, and durable immune responses and produce neutralizing antibodies while minimizing off-target effects. This is achieved with techniques such as structure-based antigen engineering, with a focus on the epitopes, e.g., displaying nanoparticles. [63]. Structure-based antigen engineering utilizes detailed structural insights into antigens and antibodies to inform antigen design, ensuring high-affinity binding to B-cell receptors. This method is particularly valuable in developing vaccines for complex or rapidly mutating viruses, such as HIV, RSV, or influenza, where slight structural variations can drastically impact immune recognition [58]. In addition, antigenicity analysis plays a supportive but significant role in vaccine design by enabling the identification and characterization of protective epitopes

on pathogens. Engineered antibodies can be tailored to map neutralizing sites or regions critical for immune evasion, providing insights into the structural and functional aspects of antigens that should be targeted by vaccines. While traditional antibodies can also be used for this purpose, engineering allows for enhanced specificity, stability, and versatility, such as creating bispecific antibodies to simultaneously bind multiple epitopes. This approach complements vaccine design by guiding the development of immunogens that elicit robust and durable protective immunity, even against rapidly mutating pathogens. However, the primary application of antibody engineering lies in improving therapeutic antibodies, and we have only clarified its more limited but relevant role in vaccine research.

Antigen structures can be visualized at atomic scales by employing high-resolution imaging techniques like cryo-electron microscopy to identify key regions likely to elicit neutralizing antibodies. A prominent example of this approach's success is the prefusion-stabilized SARS-CoV-2 spike protein, developed as the central antigen in mRNA vaccines [62]. This engineered structure significantly increased the spike protein's stability and immunogenicity, effectively enhancing the immune response against COVID-19 [63]. This achievement demonstrates how structure-based engineering can create antigens tailored to generate robust and protective immune responses [64].

Structure-based design can be applied to a wide variety of pathogens. It is important to find antibodies with desired properties, taking into account the structures in complex with their antigens to generate the correct immune response. For the influenza virus, e.g., HA and neuraminidase (NA) are promising targets for protective activity [65,66]. However, the segmented genome of influenza viruses, with the HA and NA genes located on separate segments, allows for reassortment and the emergence of novel serotype combinations among the 18 HA and 11 NA subtypes identified to date. This genetic flexibility highlights the complexity of antigenic drift and shift, emphasizing the need for antibody-guided vaccine design to target conserved epitopes across diverse and evolving serotypes. Indeed, influenza HA has been a focal point for the development of monoclonal antibody therapies and antibody-guided vaccine strategies. Early research efforts identified a conserved site on HA, known as the fusion peptide, which plays a critical role in the virus's ability to infect host cells [67]. Antibody binding to this region stabilizes its conformation and prevents viral entry, making it a promising target for therapeutic and vaccine development [68]. The identification of V(H)1-69 antibodies that broadly neutralize almost all influenza A group 1 viruses made a breakthrough in the field. It was shown that a cocktail of two antibodies (V(H)1-69 antibodies and antibodies to a highly conserved epitope in the HA) may be sufficient to neutralize most influenza A subtypes and, hence, enable development of a universal flu vaccine and broad-spectrum antibody therapies. Furthermore, unlike the highly variable globular head of HA, which encodes the 16 serotypes, the fusion peptide is conserved, making it an attractive target for broad neutralization [69,70]. Recently, Beukenhorst et al. showed that the human monoclonal antibody CR9114 targets a highly conserved epitope on the stem domain of H5 hemagglutinin, potently neutralizing diverse H5 viruses and providing proof of concept for broad pre-exposure protection against A(H5N1) infection via intranasal administration, even in the presence of pre-existing immunity [71]. Holliger et al. were the first to describe the use of bispecific antibody fragments (BsAbs, diabodies) to recruit the full spectrum of antibody effector functions, including complement activation, phagocytosis, and enhanced cytotoxicity, by retargeting serum immunoglobulins [21]. They recognize two different epitopes, allowing for the simultaneous blocking of two different signaling pathways, dual targeting of different mediators, or delivery of payloads to target sites. Another study also described the use of bispecific recombinant antibodies [72]. The authors described their application against host

IgG to redirect antigens (influenza) to host antibodies containing an Fc domain to elicit opsonophagocytosis (cellular immunity).

This breakthrough in understanding HA's conserved regions informed the design of improved vaccines that induce antibodies targeting the HA stalk instead of the variable head. In addition, these findings, supported by structural and functional analyses of monoclonal antibodies, underscore the role of antibody studies in identifying relevant epitopes, such as the fusion peptide, for vaccine design, along with the synergy between antibody research and the development of universal influenza vaccines, offering insights into broad-spectrum immunity.

4.2. Epitope-Based Vaccine Design

Another component of rational antigen design is epitope-focused design, which concentrates the immune response on specific regions or epitopes critical to viral neutralization [60]. This approach is especially useful for combating viruses that evolve quickly, as it directs the immune response toward conserved regions that are less prone to mutations. Vaccines can induce broadly neutralizing antibodies that offer cross-strain protection by targeting these stable areas [63]. For example, influenza vaccines have used epitope-focused design to target the conserved stem region of the HA protein, aiming for immunity across multiple influenza strains. This strategy enhances the breadth of immune protection and reduces the need for frequent vaccine updates caused by viral antigenic drift [63].

A parallel strategy in antibody-guided vaccine design involves creating vaccines that mimic critical neutralizing antibody epitopes. By presenting epitopes that resemble the viral structures targeted by neutralizing antibodies, these vaccines effectively train the immune system to recognize and respond to these regions, leading to highly specific and protective antibody responses [61]. Techniques for mimicking neutralizing antibody epitopes include engineered proteins, peptide scaffolds, and synthetic approaches that stabilize these epitopes in accurate and accessible configurations [73,74].

One of the primary goals of mimicking neutralizing antibody epitopes is to steer the immune system toward generating high-affinity, protective antibodies specific to crucial viral structures. For instance, HIV vaccine development has focused on designing immunogens that mimic the virus's envelope protein, particularly the CD4 binding site, a primary target of neutralizing antibodies. Exposing the immune system to these carefully crafted mimics encourages the production of antibodies that neutralize the virus by targeting its vulnerable sites. By directing the immune response to these highly specific epitopes, vaccines can achieve enhanced effectiveness against challenging pathogens [61].

Broadly neutralizing antibodies (bNAbs) for HIV have garnered significant interest due to their ability to mediate protection in primate models and their potential for therapeutic and prophylactic applications. These antibodies target well-defined epitopes on the HIV envelope glycoprotein, such as the CD4 binding site, the V2 apex, and the MPER region [75]. A key aspect of bNAb development is understanding their ontogeny, as these antibodies typically arise late in infection. Research has shown that early B-cell clones, which initially lack HIV-binding capabilities, require extensive somatic hypermutation and clonal selection to acquire the necessary affinity and breadth. This process involves expanding non-HIV-binding B-cell precursors and further stimulating them to accumulate favorable mutations that result in broadly neutralizing activity [76,77]. Escolano et al. also applied the strategy in mice and macaques to induce broadly neutralizing antibodies directed against HIV-1. They demonstrated that vaccination could induce heterologous neutralizing antibodies [78]. However, multiple off-target antibodies were also induced, indicating that sequential immunization regimens for HIV-1 vaccines need to be improved. Adjuvants and structural vaccinology play crucial roles in HIV and influenza. Adjuvants

enhance the immune response by promoting higher antibody titers and enhancing bNAb production [79,80]. Structural vaccinology, meanwhile, focuses on designing immunogens with specific shapes and presentations that have better exposed conserved viral regions. This approach allows research to "shape" the immune response and enhance the chances of producing effective, long-lasting antibodies [81].

Developing vaccines for viruses like HIV and influenza, which mutate frequently and evade immune defenses, remains a challenge. Approaches such as targeting conserved epitopes, eliciting broadly neutralizing antibodies, and employing sequential immunization approaches have shown promise in overcoming these barriers. Furthermore, despite the difficulties, there has been huge progress in the development of antibody-guided vaccines that could ensure protection against rapidly evolving viruses.

This concept underscores the importance of designing vaccines capable of priming and guiding the maturation of such B-cell lineages to generate bNAbs in individuals. Efforts to incorporate sequential immunogens that mimic the natural development of bNAbs represent a promising approach. Further exploration of these mechanisms and targeted strategies can inform the next generation of HIV vaccines and provide a robust foundation for addressing other rapidly mutating pathogens.

To achieve stable epitope conformations, essential for vaccines that mimic neutralizing antibody targets, some techniques could be employed, such as computational modeling and protein engineering. With them, epitopes that maintain their native, stable conformations can be created. Therefore, vaccines could be effective even against pathogens that alter their surface structures to avoid immune detection [82]. In SARS-CoV-2 vaccines, stabilizing the spike protein in its prefusion state was essential for eliciting potent neutralizing antibodies. This breakthrough was pivotal in guiding the immune system to generate a robust and durable response against the virus [64].

Accessibility and immunogenicity are also critical in designing effective epitope-based vaccines. The identification of T- and B-cell epitopes is a critical aspect of vaccine development, enabling the design of targeted immunogens that elicit robust immune responses. Recent advances have focused on constructing concatemers of T- and B-cell epitopes as vaccine candidates, which combine multiple antigenic regions to enhance immunogenicity. However, a significant challenge lies in the structural nature of epitopes. While linear epitopes are easier to produce and incorporate into vaccine constructs, most epitopes are conformational, requiring specific three-dimensional structures to be properly recognized by the immune system. This limitation often reduces the efficacy of epitope-based vaccines [83]. For instance, studies on FMD virus have shown that even small conformational changes in epitopes can profoundly affect vaccine efficacy, underscoring the importance of preserving structural integrity during vaccine development. In 2024, Li et al. demonstrated that the correct 3D conformation of the viral surface proteins in vaccines is crucial for antibody-mediated neutralization of FMD virus [27]. Their study will help and guide the structure-based design of new broad-spectrum and stable vaccines for protection against FMD. Addressing these challenges through innovative approaches to stabilize and present conformational epitopes will be crucial for the success of epitope-based vaccine strategies, particularly in the context of antibody-guided vaccine design. This aspect of vaccine development aligns well with the broader themes of the review and warrants further discussion [27].

Presenting epitopes in a manner that ensures they are accessible to B cells while also maximizing their immunogenic potential enhances the likelihood of a strong antibody response. So far, data show that epitope vaccines provide maximal therapeutic efficacy with minimal side effects, but the main challenge is the ability to focus the immune response on evolutionarily conserved antigenic regions.

In Figure 1, we present integrated computational pipeline (for SARS-CoV-2) epitope prioritization.

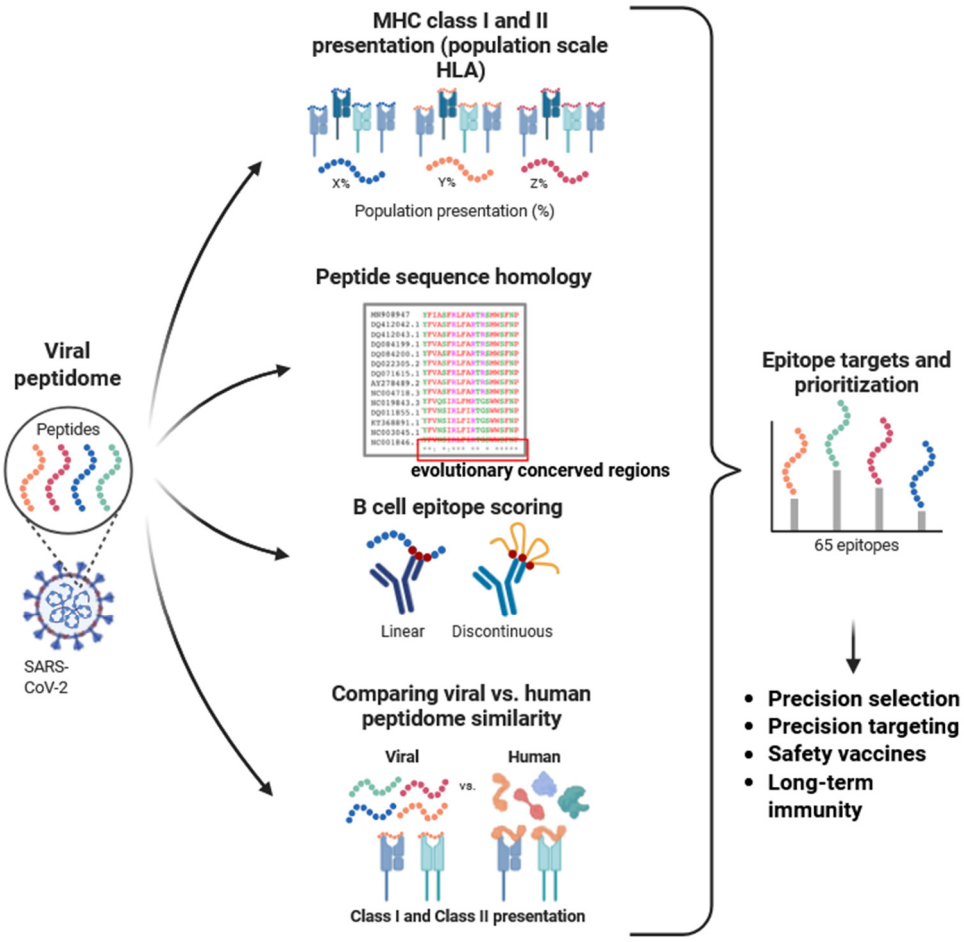


Figure 1. Integrated computational pipeline for SARS-CoV-2 epitope prioritization. In the figure, regions with evolutionary stability are marked with stars. They are biologically meaningful for prioritizing the epitopes and designing efficacy vaccines. Epitope prioritization enables precision selection and targeting, ensuring safer vaccines and promoting long-term immunity. Created in BioRender. Velikova, T. (2025) https://BioRender.com/354fa7n. (accessed on 25 May 2025).

4.3. Nanoparticle-Based Vaccines Design

Nanoparticles possess specific biological characteristics and facilitate the inclusion of antigens, making them very convenient in the development of vaccines [84]. Thus, the immunogen can be exposed to the immune system similar to that delivered by the virus and induce an immune response. Nanoparticles allow for targeted presentation and prevent the antigenic material from disintegrating or triggering a local response [85].

Nanoparticle display is a relatively novel approach in which antigens are presented on nanoparticles to boost immunogenicity; by displaying antigens in a multivalent form, nanoparticle display mimics the repetitive structures found on viral surfaces, an arrangement that is highly effective at stimulating B-cell activation [86,87]. This methodology has shown encouraging results in preclinical studies of RSV and SARS-CoV-2 vaccines, where nanoparticles displaying multiple copies of antigens resulted in potent antibody responses. Nanoparticles can also be engineered to display different antigens, creating multivalent vaccines capable of simultaneously targeting numerous strains or types of pathogens. This versatility enables nanoparticle-based vaccines to respond effectively to diverse and evolving viral threats [88].

A very recent study has shown that recombinant NA antigens can be enhanced in immunogenicity by being presented multivalently on a nanoparticle carrier [89]. The authors confirm the efficacy of nanoparticles as a vaccine platform and demonstrate their ability to elicit a strong humoral immune response against two highly divergent subtypes of influenza A. Different NPs have been used to deliver a wide range of antigens, such as hepatitis B virus [90], Bacillus anthracis [91], tetanus toxoid [92], HBV antigens [93], and many others. NPs are extremely useful because they can function as a delivery system and as immunostimulatory adjuvants [94]. Their use for delivering vaccine components is of great importance, as they can easily encapsulate target antigens, deliver them precisely, provide sustained and specific release by crossing biological barriers, and induce a long-lasting immune response [95].

4.4. Scaffold-Based Vaccine Design

Scaffold-based designs and synthetic scaffolding techniques can present epitopes in configurations that maximize immune exposure and promote the generation of high-affinity antibodies. HIV vaccines have effectively used scaffold-based designs to focus immune responses on specific epitopes, particularly on the virus's envelope protein, with encouraging results in generating strong immune responses [74]. In 2019, Hessell et al. demonstrated multimeric epitope–scaffold HIV vaccines [96]. They demonstrated that polyfunctional antibodies can be generated and thus may provide a reduced risk of acquisition and better viral control, which would be a major advantage, especially in areas where the incidence of HIV infection is high.

Antibody-guided vaccine design, leveraging rational antigen design and neutralizing epitope mimicry, is shaping a new era of vaccine effectiveness and precision. Rational antigen design strategies—including structure-based engineering, epitope-focused design, and nanoparticle display—enable the development of vaccines that target the immune system with high specificity and durability [58]. Mimicking neutralizing antibody epitopes further directs immune responses toward viral structures most susceptible to neutralization, generating potent, targeted immune defenses [61]. These advanced approaches promise to improve vaccine efficacy and adaptability, making them more responsive to rapidly evolving pathogens and paving the way for vaccines that provide enhanced, long-lasting protection [62].

4.5. SARS-CoV-2 Vaccines: Mechanisms of mRNA and Protein-Based Platforms

SARS-CoV-2, the virus responsible for COVID-19, uses its spike (S) protein to bind to ACE2 receptors in human cells, initiating infection. This spike protein has become the primary target for vaccine development, as inducing an immune response against it can neutralize the virus and prevent cell entry [97]. Both mRNA and protein-based SARS-CoV-2 vaccines leverage spike protein epitopes to prompt an immune response, specifically by inducing neutralizing antibodies that bind to the virus and block infection. mRNA vaccines, such as those developed by Pfizer-BioNTech and Moderna, deliver a synthetic strand of mRNA encoding the SARS-CoV-2 spike protein into host cells. This mRNA is encapsulated within lipid nanoparticles to facilitate delivery to cells, where host ribosomes translate it into the spike protein, which is then presented on the cell surface, stimulating an immune response and producing neutralizing antibodies and memory B cells. These neutralizing antibodies specifically target regions on the receptor-binding domain (RBD) of the spike protein, blocking viral attachment to ACE2 receptors and thereby preventing infection [97]. Protein-based vaccines, such as Novavax's SARS-CoV-2 vaccine, deliver the spike protein directly rather than using a genetic template. Novavax's vaccine uses recombinant nanoparticle technology to create a stable form of the spike protein, which

includes specific epitopes that are highly immunogenic. These protein subunit vaccines prompt an immune response by directly exposing immune cells to the spike protein's epitopes, producing neutralizing antibodies. Adjuvants are often added to improve the immune response, as seen in Novavax's use of Matrix-M adjuvant, which increases both the magnitude and durability of antibody production [98,99]. Both vaccine types focus on epitopes within the RBD and other conserved regions of the spike protein. These epitopes are specifically selected because they are accessible to antibodies and critical for viral attachment and entry. By targeting these specific regions, mRNA and protein-based vaccines stimulate the immune system to produce neutralizing antibodies that effectively block the virus from binding to ACE2 receptors on human cells, thus preventing infection [100]. Both mRNA and protein-based SARS-CoV-2 vaccines use spike protein epitopes to induce neutralizing antibodies. The primary difference between the two types of vaccines lies in the delivery method: mRNA vaccines use the cellular machinery in the host to produce the spike protein, whereas protein-based vaccines introduce the spike protein directly. Both approaches, however, have demonstrated significant efficacy in targeting crucial spike protein regions to induce immunity.

5. Challenges and Limitations in Antibody-Guided Vaccine Design

Just as vertebrates have evolved various defense mechanisms against pathogens, the pathogens have evolved various options for evading the host's normal defenses [101–105]. Most of them use one or more strategies to evade the immune system. For example, HIV uses a combination of them and manages to defeat the immune response [106]. Antigenic variation is one way an infectious agent can evade immune surveillance. The reason is that when the agent encounters the host's immune responses, it must overcome or avoid the innate and adaptive immune responses to establish infection successfully. So, changing its antigens allows pathogens to escape from immunity [107,108].

There are several possibilities for the occurrence of antigenic variation, considering the diversity of the antigenic types of the infectious agents, the presence of the large set of unprotected hosts, and possible rearrangements in the genetic material of the pathogen. Most infectious agents exist in a wide variety of antigenic serotypes, viruses specifically but not only. For example, over 90 known types of Streptococcus pneumoniae cause bacterial pneumonia [109,110]. However, each serotype differs from the others in the structure of its polysaccharide capsule [111] and causes the disease many times in the same host. Infection with a given serotype can result in specific immunity that protects against reinfection, but not with a different serotype. Therefore, to the adaptive immune system, each serotype of a given pathogen represents a distinct infectious agent.

A second mechanism of antigenic variation is associated with the exhaustion of potential unprotected hosts if it has not evolved at least two different ways of changing its antigenic type. For example, when infected with influenza, the human population gradually develops a protective immunity to this type of virus through neutralizing antibodies against the main surface protein [112]. It turns out that its survival depends on having a lot of unprotected individuals. Thus, the virus has evolved to use two strategies: antigenic drift and antigenic shift. Antigenic drift is caused when point mutations occur in genes encoding surface proteins (e.g., in influenza, these are HA and NA) [113,114]. They allow the virus to evade neutralizing antibodies. Some mutations affect epitopes that are recognized by T cells. Thus, the cells infected with the mutant virus are also not destroyed, and the virus spreads. Immunized and those who have passed the disease against it are susceptible to a new variant [115]. Antigenic shift occurs when there is a recombination of the fragmented genetic material of the virus. Influenza may contain segments of some other animal influenza viruses. This also leads to major changes in the structural proteins on the surface

of the virus, and these are recognized poorly or not at all by antibodies and T cells directed against the first variant [116,117]. Therefore, viruses continuously accumulate genetic changes in the epitopes of their major surface proteins. This helps them to evade immune recognition and necessitates updates to the antigens included in the vaccines.

Antigenic variation is also associated with programmed rearrangements in the pathogen's genetic material. The mechanism is best described in African trypanosomes, where reinfection occurs after changes in the surface antigen. The trypanosome has a type of variant-specific glycoprotein (VSG), which leads to a protective antibody response. The VSG gene can be altered by gene rearrangement, which leads to different VSG glycoproteins [118,119]. If several trypanosomes with altered surface glycoproteins escape the antibodies, they grow and cause a disease relapse. Malaria is another disease associated with changes in the antigens of the causative agent to avoid elimination by the immune system.

Considering the repeated exposures to some pathogens, we should also mention the immune imprinting. In such cases, the immune system must decide whether to recall already established antibodies to the original variant or produce new antibody responses specific to the new variant. In fact, this mechanism has a dual potential—it can hinder the immune system against a disease. Still, it can also enhance immune responses against it [120]. Given its role in shaping humoral responses after repeated infections with antigenically altered viruses, its impact should be carefully considered when designing vaccination strategies. In recent years, in the COVID-19 pandemic, we have seen the emergence of many variants with immune escape mutations. This led to numerous updates and modifications to the COVID-19 vaccines. All of them were intended to improve the efficacy of the vaccine against circulating variants, but sometimes in combination with another pathogen, leading to the induction of cross-responses that are not specific [121,122].

A complete understanding of immune imprinting is of great importance to guide vaccine design. Ultimately, vaccine effectiveness against current and future viral infections is of the utmost importance in limiting the spread, morbidity, and mortality. A possible potential risk associated with vaccine development is antibody-dependent enhancement of disease (ADE). Antibody-mediated immune responses induced by vaccination can facilitate productive infection and viral dissemination and increase disease severity. This phenomenon has been described in some viruses as dengue, Zika, and HIV [123–125], but it also appears to occur with SARS-CoV-2 [126]. So, ADE can be considered an alternative approach to viral infection of cells [127]. In cases where viruses can mediate ADEs, many antibodies may provide protection. The antibody quantity and titer are fundamental because the antibody concentrations may be pathogenic rather than neutralizing [128]. AED should be carefully evaluated in developing new vaccines already in preclinical studies and models to create safe and effective vaccines.

In Table 1, we present some aspects of the advances and limitations in immunological strategies for antibody-guided vaccine design.

Table 1. Advances and limitations in immunological strategies for antibody-guided vaccine design.

Immunological Strategy	Advances	Limitations	Ref.
Monoclonal antibodies (mAbs)	-Highly specific and potent antiviral agents targeting specific epitopes on viral proteins (e.g., SARS-CoV-2).	-Expensive and time-consuming to develop and manufacture at scale.	[12,129]
	-Proven efficacy in reducing viral load and symptoms in infected patients (e.g., for COVID-19).	-Limited efficacy against emerging variants due to viral mutations.	

Table 1. *Cont.*

Immunological Strategy	Advances	Limitations	Ref.
	-Can be used as both a therapeutic and a prophylactic strategy.	-Risk of viral escape mutants and immune evasion.	
Nanoparticle-based vaccines	-Enhanced immune responses due to increased surface area and ability to mimic natural virus structures.	-Potential for unforeseen toxicities due to nanomaterial accumulation or immune overactivation.	[130]
	-Able to present multiple epitopes, enhancing cross-protection against different strains.	-Scalability and manufacturing challenges.	
B-cell and T-cell epitope-based vaccine design	-Targeting conserved viral epitopes can help design broad-spectrum vaccines, protecting against various strains.	-Limited ability to predict the immunodominant epitopes across diverse populations.	[78,131]
	-Improves immune recognition and long-term immunity (via memory B and T cells).	-Immunological complexity can lead to incomplete or suboptimal responses.	
Adjuvants in vaccine formulation	-Adjuvants enhance the strength and duration of immune responses, improving viral neutralization.	-Some adjuvants may cause unwanted inflammation or adverse effects.	[132]
	-Used to boost responses to suboptimal vaccine candidates, enabling better protection.	-Variability in efficacy between individuals and populations (e.g., in immunocompromised patients).	
Viral vector-based vaccines	-Efficient delivery of foreign genetic material for producing viral antigens (e.g., adenovirus-based vaccines).	-Potential pre-existing immunity to the viral vector, reducing vaccine efficacy.	[133]
	-Proven success with rapid development (e.g., JNJ-78436735 or Ad26.COV2.S of Johnson & Johnson; AstraZeneca vaccines—AZD-1222 or ChAdOx1 nCoV-19).	-Risk of vector-induced immune responses and safety concerns in certain populations (e.g., in immunocompromised).	
Immune checkpoint inhibition	-Can enhance immune responses against persistent viral infections, boosting neutralizing-antibody production.	-Potential for autoimmunity and serious side effects due to uncontrolled immune activation.	[134]
	-Helps overcome immune suppression by viruses (e.g., HIV and Hepatitis C).	-Long-term safety and efficacy remain uncertain, especially in non-cancerous contexts.	
RNA-based vaccines	-Enables fast and adaptable vaccine development by encoding antigenic proteins directly (e.g., mRNA vaccines for COVID-19).	-Stability concerns and need for ultra-cold storage for some formulations.	[9,135]
	-Induces both humoral and cellular immunity, enhancing long-lasting protection.	-Potential for rare side effects and adverse immune responses, especially in certain populations.	

Immune checkpoint inhibition, traditionally associated with cancer immunotherapy, has emerged as a potential strategy in vaccine design. Immune checkpoints, such as PD-1/PD-L1 and CTLA-4 pathways, modulate the balance between immune activation and tolerance. In the context of vaccines, transient checkpoint inhibition can enhance immune responses by promoting T-cell activation and increasing the generation of high-affinity antibodies [136]. Preclinical studies have demonstrated that immune checkpoint blockade can improve the efficacy of vaccines by enhancing germinal center formation, which is critical for robust B-cell maturation and antibody production. For example, blocking PD-1 signaling during vaccination has been shown to increase the breadth and durability of antibody responses against viral pathogens [137,138].

However, this strategy requires careful optimization to avoid excessive immune activation or autoimmune complications. Integrating checkpoint inhibitors into vaccine regimens offers a promising avenue to boost immunogenicity, particularly in populations with weakened immune responses, such as the elderly or immunocompromised individuals. Further research is needed to explore this approach in diverse vaccine platforms, ensuring safety and efficacy. Additional strategies listed in Table 1, such as adjuvant engineering and epitope stabilization, also play significant roles in enhancing the performance of antibody-guided vaccines, and their inclusion is supported by growing evidence in the literature.

6. Emerging Techniques in Immunological Vaccine Design

6.1. High-Throughput Screening for Epitope Discovery

Single B-cell sorting is a promising method for interrogating immune responses to vaccination or infection. It is the most frequently used method for the characterization of antigen-specific B cells in human samples [139,140] and can help show the link between the immune system and neurodegenerative diseases [141]. The aim of the technology is to identify paired heavy- and light-chain B-cell receptor (BCR) sequences from antigen-specific B cells.

The most modern approach, however, is different—linking B-cell receptors to antigens specificity through sequencing [142]. This is an approach in which a high-throughput mapping is performed for paired light-chain and heavy-chain BCR sequences to their cognate antigen specificities. This aims to compensate for limitations of the single B-cell sorting with fluorescent antigen baits. The technology of Libra-seq applies methods from bioinformatics to map antigen barcodes to single cells, and it can recover not only antigen specificity but also the light and heavy BCR chains. Using LIBRA-seq, Setliff et al. mapped the antigen specificity of thousands of B cells from two HIV-infected subjects [142]. They confirmed the predicted specificities for two well-known HIV-specific bNab lineages and for a number of influenza-specific antibodies.

The bioinformatics approach was nicely summarized by He et al. [143], describing preprocessing, normalization, and data quality control. Next is the application of well-known methods from statistics, such as principal component analysis for data dimension reduction as a preprocess step for nonlinear methods for dimensionality reduction, such as t-distributed stochastic neighbor embedding [144]. Uniform manifold approximation and projection (UMAP) [145] is better at representing the topology of the data, but it is also a stochastic algorithm, and different runs may have different results.

Part of the process is the batch correction process, the aim of which is to preserve the biological heterogeneity. An important stage of the analysis is cell clustering with various algorithms to identify shared traits (expression profiles) between cell populations and to group them accordingly.

6.2. Computational Modeling and Machine Learning

Bioinformatics in the study of the immune system naturally evolved into the application of methods from machine learning for predicting the antibody–virus interaction, which was applied very successfully in the SARS pandemic [146]. This approach includes molecular dynamics simulation with a 3D model of an antibody and proteins from the binding receptor of the SARS-CoV-2 virus, providing numerical integration and an optimization procedure to calculate the interaction. Another part of this type of analysis is a calculation of the energy of the contact between the antibody and the RBD domain of the virus, using some approximate techniques from quantum field mechanics, such as the Particle-Mesh Ewald (PME) method [147]. Computational modeling and machine learning enable the

prediction of antigen–antibody interactions and the identification of protective epitopes. These approaches complement antibody-guided strategies by streamlining the selection of targets with high neutralization potential, ultimately accelerating the development of vaccines with enhanced efficacy and broader coverage.

Other approaches and corresponding software are thoroughly and systematically enumerated by Norman et al. [148]. They range from raw data processing and numbering to antibody-specific loops, epitope prediction, and full FV modeling. The newest and most powerful approaches are related to deep learning [149–151]. The power of deep learning to capture complex nonlinear relationships in high-dimensional datasets is perfectly suited for biology and especially for investigating the immune system and its interactions with pathogens via antibodies. The spectacular success of the multitude of vaccines for SARS-CoV-2 is direct proof of the potential of this approach to surpass any other in the field of computational methods [152]. The success of this approach is highly dependent on data and their public sharing, which has to be encouraged and fostered through careful investment in database creation and maintenance by different public and private entities.

7. Vaccine Platforms and Future Directions in the Application

7.1. Next-Generation Vaccine Platforms

Vaccine platforms evolve rapidly. The most promising technologies for antibody-guided vaccines are self-amplifying RNA (saRNA) and viral vector-based platforms. The former utilizes a viral RNA construct to encode the antigen and amplify the immune response. Therefore, saRNA is a potent inducer of sustained immune responses. Furthermore, these new platforms enhance efficacy by generating robust antibody responses, with improved breadth and durability of immune responses, while using a lower antigen dose, reducing vaccine production cost and improving stability. These approaches are especially useful for pathogens with highly variable antigens, such as influenza and coronaviruses [153,154]. Incorporating antibody-guided design into these platforms allows for the inclusion of structurally characterized epitopes, ensuring vaccines elicit precise and protective immune responses. This integration enhances the adaptability of these platforms to rapidly evolving pathogens, making them invaluable in combating emerging infectious diseases.

The other type, viral vector-based vaccines, uses modified viruses to deliver genetic material that encodes the target antigen. These vaccines can also elicit strong cellular and humoral immune responses, including generating antibody-mediated protection. For example, viral vectors that employed adenoviruses have succeeded in several high-profile vaccines, including those for vector-based COVID-19 vaccines. These platforms illustrate, once again, their potential to accelerate the development and deployment of antibody-guided vaccines. Moreover, the flexibility of viral vectors allows for integrating multiple antigens, supporting the design of vaccines that can target various strains of a virus or a broader range of pathogens. Although their mechanisms differ, both saRNA and viral vector-based platforms are promising in developing next-generation antibody-guided vaccines, particularly for emerging infectious diseases. This means that these technological advancements could allow for faster, more effective, and safer responses to global health threats [133].

7.2. Personalized Vaccines Based on Immunogenetics

Another exciting aspect of the development of antibody-guided vaccines lies in immunogenetics. This is related to the creation of personalized vaccines designed according to the genetic and immune profile of a certain individual. If vaccine engineering is based on immunogenetics, we can expect further advances in optimizing antibody responses

and, thus, enhancing vaccine efficacy. The idea is to customize vaccine formulations based on a person's genetic makeup, including variations in major histocompatibility complex (MHC) genes, immune cell receptors, and other genetic factors that influence immune responses [155]. By identifying conserved epitopes recognized by broadly neutralizing antibodies, vaccines can be tailored to overcome genetic diversity in immune responses. This synergy between immunogenetics and antigenicity analysis ensures vaccines are effective across diverse populations, leveraging insights into host–pathogen interactions for optimal immunogenicity.

Furthermore, it is hypothesized that individuals with different genetic backgrounds can exhibit varying immune responses to the same vaccine (i.e., due to polymorphisms in immune-related genes such as interleukins (e.g., IL-10), Toll-like receptors (TLRs), and Fc receptors), which can affect how the organism responds to vaccine antigens and adjuvants. By identifying and incorporating these genetic variations, personalized vaccines could improve the effectiveness of vaccines developed by antibody-guided strategies, reducing the need for a one-size-fits-all approach. This could lead to more efficient vaccine designs that elicit stronger, longer-lasting immunity in diverse populations [156]. For example, personalized vaccines could address the high variability in diseases, such as cancer and HIV, where individual immune profiles can greatly impact treatment outcomes. Integrating immunogenetic data into vaccine design promises to optimize antibody production and mitigate potential adverse effects, providing a more targeted and effective approach to immunization [157].

8. Conclusions

The development of many-system approaches and the collection of big science datasets have allowed for a much better understanding of the immune responses that are elicited following vaccination. Consequently, we can now use key antigen conformations, epitopes, etc., with much greater precision for developing the vaccines.

Antibody-guided vaccine strategies have advanced in recent years during the COVID-19 pandemic by promising to enhance viral neutralization and robust protection against various infectious diseases. Antibody-guiding can improve vaccine design for increased specificity and potency of antibodies that neutralize pathogens, offering more precise and effective immune responses and, therefore, protection. The ability to tailor these vaccines for improved antibody efficacy—through strategies such as antigenicity analysis, immune modulation, and novel adjuvants—can significantly boost vaccine performance, particularly in the face of rapidly evolving viruses. The "Goldilocks immunity" and "immuno-wave" models provide frameworks to better understand the balance between immune activation and regulation, essential for designing vaccines that achieve optimal protection without inducing harmful immune responses.

The approaches reviewed here are essential to realizing the full potential of precision vaccines. Despite progress, several challenges must be solved to optimize these strategies, including variability in individual immune responses, limited understanding of long-term immunity, and the complexity of producing vaccines that can consistently induce strong neutralizing antibodies for diverse populations. None of the strategies described has proven to be a universal solution to date, but each of the presented strategies considers the approach, the target pathogen, and the expected immune response. However, developing next-generation vaccine platforms, such as self-amplifying RNA and viral vectors, is our chance to gain protection against emerging and re-emerging viral threats. Advances in immunogenetics, personalized vaccine approaches, and cutting-edge vaccine technologies offer exciting opportunities for optimizing antibody-guided vaccine strategies.

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