ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2026.1102
Asthma Allergy Immunol 2026;24:1-12

REVIEW

Received: 08.10.2025 • Accepted: 23.12.2025
Online Published: 02.03.2026

Immunological Mechanisms of COVID-19 Vaccines: Implications for Respiratory and Allergic Populations

Hamidia MAULANINGTYAS[1], Resti YUDHAWATI[2,3,4], Alfian Nur ROSYID[2,3,4]

[1] Pulmonology and Respiratory Medicine Residency, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3] Department of Pulmonology and Respiratory Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[4] Department of Pulmonology and Respiratory Medicine, Universitas Airlangga Hospital, Surabaya, Indonesia

Corresponding Author: Resti Yudhawati ✉ resti.yudhawati2021@gmail.com; resti-y-m@fk.unair.ac.id

ABSTRACT

The COVID-19 pandemic has highlighted the pivotal role of vaccination in reducing global morbidity and mortality, with vaccine efficacy underpinned by complex immunological mechanisms that coordinate both immediate and long-term protection. Innate immunity provides the first line of defense through pattern recognition receptors, type I interferons, and proinflammatory cytokines, while dendritic cells bridge this early response to adaptive immunity by presenting antigens to naïve T lymphocytes. This process initiates the differentiation of $CD4^+$ helper subsets, $CD8^+$ cytotoxic T cells, and B cells, leading to antibody production, affinity maturation, and the establishment of durable immunological memory. Complementing these mechanisms, the phenomenon of hybrid immunity—arising from the combination of natural infection and vaccination—has been shown to generate qualitatively superior protection, characterized by higher titers of cross-neutralizing antibodies, broader memory B cell repertoires, and sustained T cell activity, thereby offering enhanced resilience against emerging variants such as Delta and Omicron. At the same time, individuals with chronic respiratory diseases and allergic predispositions represent a vulnerable subgroup whose responses may be influenced by underlying inflammation, immunomodulatory therapy, or hypersensitivity to vaccine components, with rare but notable adverse events such as polyethylene glycol–related anaphylaxis and transient respiratory exacerbations underscoring the need for tailored vaccination strategies. By synthesizing current immunological insights, this review emphasizes the interplay between innate and adaptive responses, the synergistic benefits of hybrid immunity, and the clinical considerations for at-risk populations, thereby supporting the development of inclusive, adaptive, and evidence-based vaccination approaches that address the evolving challenges of SARS-CoV-2 and ensure equitable protection across diverse global settings.

Keywords: COVID-19 vaccines, innate immunity, adaptive immunity, hybrid immunity, immunological memory

INTRODUCTION

COVID-19 vaccination has become a central pillar of global pandemic control, offering substantial protection against severe disease and mortality. The immunological mechanisms underlying vaccine efficacy—such as activation of dendritic cells, T cell-mediated cytotoxicity, and B cell-driven antibody production—have been well-characterized in general populations (1,2). However, individuals with chronic respiratory conditions and allergic predispositions represent a clinically distinct subgroup whose vaccine responses may be modified by underlying inflammation, immunomodulatory therapy, or hypersensitivity to vaccine components (3,4).

For example, polyethylene glycol (PEG), an excipient in mRNA vaccines, has been associated with rare but serious allergic reactions, including anaphylaxis (5). Additionally, patients with asthma or COPD may experience transient respiratory exacerbations following vaccination, as reported in observational studies (6). These findings highlight the need for stratified immunogenicity data and tailored vaccination protocols for vulnerable populations (5,6).

ORCID Hamidia Maulaningtyas / 0009-0002-4751-7173, Resti Yudhawati / 0000-0002-0808-8524, Alfian Nur Rosyid / 0000-0001-7042-996X

From an international perspective, this issue is particularly relevant in regions where respiratory diseases are prevalent but underdiagnosed, and where vaccine guidelines may not fully account for allergic risk profiles. The underrepresentation of these groups in clinical trials limits the generalizability of safety and efficacy data, creating gaps in global vaccine equity and implementation. Hill et al. emphasized that diversity in vaccine trials remains limited, especially for individuals with chronic conditions and allergic risks (7). Similarly, Pepperrell et al. argued that inclusive trial design is essential to ensure vaccine effectiveness across varied populations (8). In Southeast Asia, Sinuraya et al. highlighted how underdiagnosis and vaccine hesitancy intersect in respiratory cohorts, reinforcing the need for context-specific strategies (9).

By reporting immunological insights and clinical considerations specific to respiratory and allergic cohorts, this manuscript contributes to a more inclusive and evidence-based approach to COVID-19 vaccination worldwide. Accordingly, this study aims to synthesize current immunological evidence and clinical observations to inform safer, more adaptive, and globally relevant vaccination strategies.

MECHANISM OF ALLERGY TO COVID-19 VACCINES

In addressing the global impact of the COVID-19 pandemic on public health, vaccination has emerged as one of the most effective strategies to reduce morbidity and mortality rates. Behind the success of vaccination lies a complex immunological mechanism that contributes to the development of protective responses against SARS-CoV-2, including the activation of T cells, antibody production by B cells, and the formation of long-lasting memory cells (1). A comprehensive understanding of the immunological principles of COVID-19 vaccines is essential for healthcare professionals, as well as for guiding the development of more adaptive vaccines in response to ongoing viral mutations (2).

The following discussion will systematically explore the components of innate and adaptive immunity activated by COVID-19 vaccines and examine the phenomenon of hybrid immunity as a broader and more durable immune response resulting from the combination of natural infection and vaccination (10).

Innate Immunity

Innate immunity serves as the body's first line of defence against SARS-CoV-2 and plays a pivotal role in shaping the overall immune response to COVID-19 vaccines. Unlike adaptive immunity, which requires antigen-specific recognition and clonal expansion, innate immunity responds rapidly and non-specifically through cellular and molecular mechanisms involving macrophages, dendritic cells, natural killer (NK) cells, and soluble mediators such as cytokines and type I interferons (11).

COVID-19 vaccines—particularly mRNA and adenoviral vector platforms—activate innate immune pathways via pattern recognition receptors (PRRs), most notably Toll-like receptors (TLRs). For example, TLR7 and TLR8 recognize single-stranded RNA from mRNA vaccines, initiating downstream signaling cascades through MyD88 and TRIF adaptors. This leads to the activation of transcription factors such as NF-κB and IRF3/7, which drive the production of antiviral cytokines and inflammatory mediators (12).

A key outcome of this activation is the secretion of type I interferons (IFN-α and IFN-β), which induce an antiviral state in surrounding cells and enhance antigen presentation by upregulating MHC class I molecules. Concurrently, proinflammatory cytokines such as IL-6, TNF-α, and IL-1β are released, promoting immune cell recruitment and amplifying the local inflammatory response. While these cytokines are essential for vaccine efficacy, excessive release may contribute to immunopathology, underscoring the need for balanced activation (13).

Importantly, dendritic cells act as a bridge between innate and adaptive immunity. Upon activation, they migrate to lymphoid tissues, present processed antigens to naïve T cells, and initiate the differentiation of $CD4^+$ and $CD8^+$ T cells, as well as B cell activation for antibody production. This crosstalk ensures that the innate response not only provides immediate protection but also orchestrates the development of long-term adaptive immunity (11).

Emerging evidence also highlights the concept of trained immunity, wherein innate immune cells undergo epigenetic reprogramming following vaccination, resulting in enhanced responsiveness to subsequent infections. This phenomenon, observed with certain vaccine platforms, may contribute to broader protection beyond SARS-CoV-2 (14).

Adaptive Immunity

Adaptive immunity is a highly specialized arm of the immune system that provides long-lasting protection through antigen-specific responses. In the context of COVID-19 vaccination, adaptive immune activation begins with the uptake and presentation of viral antigens—primarily the spike protein—by dendritic cells. These antigen-presenting cells migrate to lymphoid tissues, where they initiate the activation of naïve T and B lymphocytes. The coordinated stimulation of both cellular and humoral components ensures a comprehensive immune response capable of neutralizing the virus and preventing disease progression. Notably, studies have demonstrated that mRNA and adenoviral vector vaccines effectively engage both arms of adaptive immunity, resulting in robust T cell responses and high titers of neutralizing antibodies (2).

Among the cellular components, $CD4^+$ T cells play a pivotal role in orchestrating the adaptive immune response following vaccination. Upon recognition of antigenic peptides presented via MHC class II molecules, naïve $CD4^+$ T cells differentiate into distinct subsets, including Th1 and T follicular helper (Tfh) cells. Th1 cells contribute to antiviral defense by secreting cytokines such as IFN-γ, which enhance macrophage activation and support $CD8^+$ T cell function. In parallel, Tfh cells localize to germinal centers and provide essential help to B cells, facilitating class switching and affinity maturation. The presence of functional Tfh cells has been strongly associated with the generation of high-affinity antibodies and sustained humoral immunity (15).

Complementing the helper functions of $CD4^+$ T cells, $CD8^+$ T cells—also known as cytotoxic T lymphocytes (CTLs)—are essential for the elimination of virus-infected cells. Following antigen presentation via MHC class I molecules, $CD8^+$ T cells undergo clonal expansion and acquire cytolytic capabilities. These effector cells release perforin and granzymes, inducing apoptosis in infected cells and thereby limiting viral replication. Importantly, COVID-19 vaccines have been shown to elicit durable $CD8^+$ T cell responses, which are particularly valuable in individuals with declining antibody levels or in the context of emerging variants. Recent evidence indicates that vaccine-induced $CD8^+$ T cells retain cross-reactivity against multiple SARS-CoV-2 variants, contributing to sustained cellular immunity (16).

In addition to cellular responses, humoral immunity mediated by B cells plays a critical role in neutralizing the virus. Upon encountering viral antigens—either directly or with assistance from Tfh cells—naïve B cells differentiate into plasma cells that secrete immunoglobulins, predominantly IgG. These antibodies target the receptor-binding domain (RBD) of the spike protein, effectively blocking viral entry into host cells. Beyond neutralization, antibodies also mediate opsonization and activate the complement system, enhancing pathogen clearance. COVID-19 vaccines, particularly mRNA-based platforms, have consistently demonstrated the ability to induce strong and persistent antibody responses, with high titers of spike-specific IgG observed across diverse populations (17).

The durability of adaptive immunity is largely attributed to the formation of immunological memory. Following the resolution of the primary immune response, a subset of activated T and B cells differentiate into long-lived memory cells. Memory T cells are categorized into central memory (TCM) and effector memory (TEM) subsets, which reside in lymphoid tissues and peripheral sites, respectively. Meanwhile, memory B cells retain the capacity to rapidly produce high-affinity antibodies upon re-exposure to the antigen. Longitudinal studies have confirmed that COVID-19 vaccines induce robust and persistent memory responses, with both memory B and T cells detectable for several months post-vaccination—even as circulating antibody levels naturally decline (18). As shown in Figure 1, dendritic cells serve as the critical link between innate and adaptive immunity, presenting antigens to naïve T cells and initiating the cascade that leads to both cellular and humoral protection (19).

Hybrid Immunity

Hybrid immunity refers to the enhanced and broadened immune protection observed in individuals who have experienced both natural SARS-CoV-2 infection and subsequent vaccination. This dual exposure activates and reinforces both arms of adaptive immunity—cellular and humoral—resulting in superior immunological outcomes compared to infection or vaccination alone (16,20,21).

Mechanistically, hybrid immunity is associated with a qualitatively superior immune response that surpasses either exposure in isolation. Individuals with hybrid immunity consistently exhibit higher titers of neutralizing antibodies, including cross-reactive antibodies capable of recognizing multiple variants of concern, such as Delta

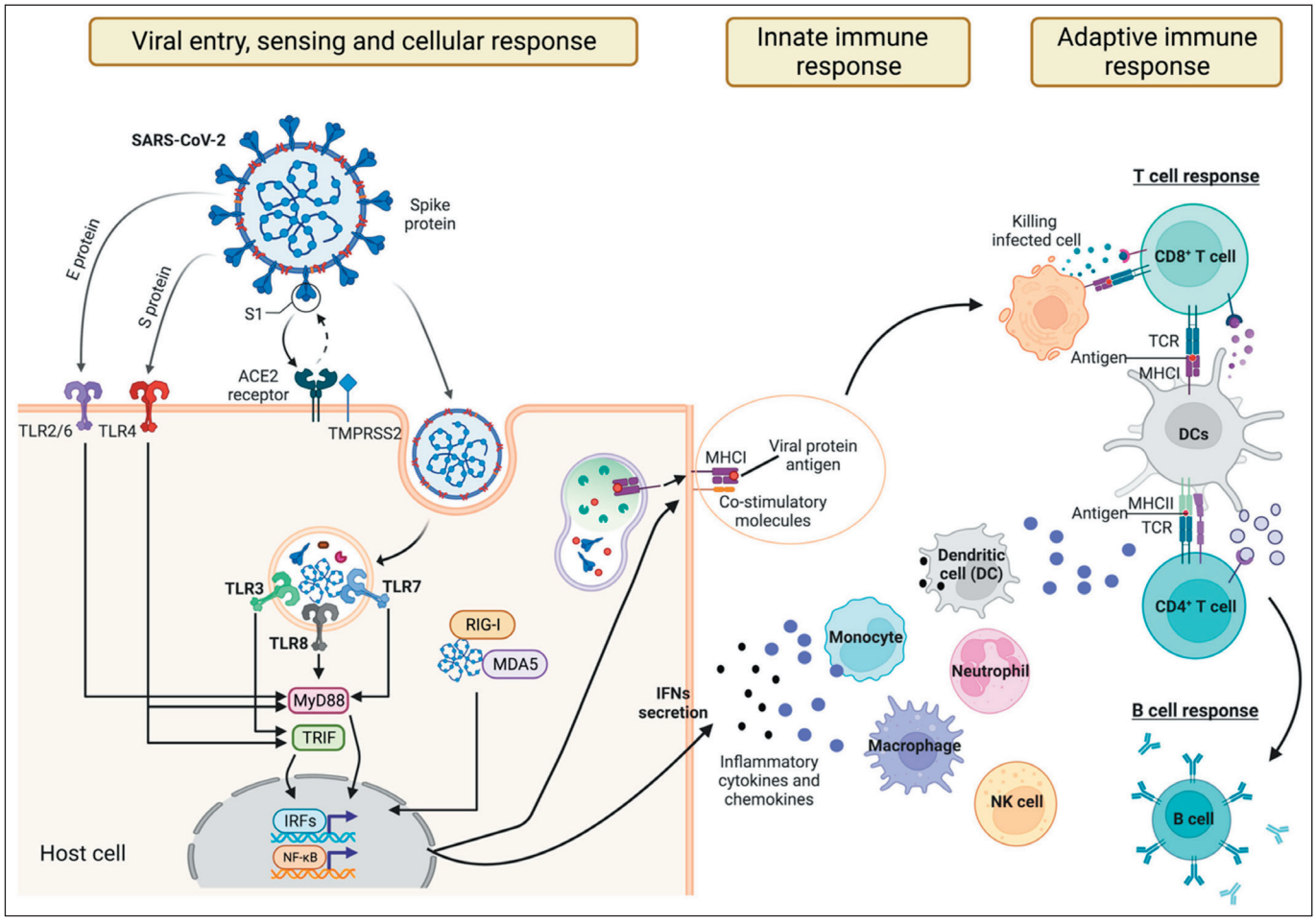

Figure 1. Immunological concept of COVID-19 vaccines: integration of innate, adaptive, and hybrid immunity. Schematic illustration of the immune responses elicited by COVID-19 vaccination. The innate immune response is initiated through recognition of vaccine components by pattern recognition receptors (PRRs), leading to the production of type I interferons, proinflammatory cytokines, and the activation of macrophages, dendritic cells, and natural killer (NK) cells. Activated dendritic cells migrate to lymphoid tissues and present antigens to naïve T lymphocytes, thereby linking innate to adaptive immunity. This process results in the differentiation of $CD4^+$ T helper subsets (Th1 and T follicular helper cells), $CD8^+$ cytotoxic T lymphocytes, and B cells, culminating in antibody production, affinity maturation, and the establishment of long-lived memory cells. Hybrid immunity, generated by the combination of natural infection and vaccination, further enhances both humoral and cellular responses, providing broader cross-variant recognition, higher antibody titers, and more durable protection compared with either exposure alone (19).

and Omicron (20). This enhanced humoral response is supported by greater memory B cell diversity and improved affinity maturation, which together contribute to the generation of more potent and durable antibodies (21). In parallel, hybrid immunity promotes robust activation of $CD4^+$ and $CD8^+$ T cells, with increased breadth and longevity of cellular immunity, including cross-variant recognition and sustained effector function (16). These synergistic enhancements across both humoral and cellular compartments underscore the immunological advantage conferred by hybrid immunity, particularly in the context of evolving viral variants (16,20,21).

Supporting this mechanistic insight, recent population-based studies have demonstrated that individuals with hybrid immunity exhibit stronger protection against symptomatic reinfection. For instance, Hall et al. showed that prior infection followed by vaccination significantly reduced the risk of reinfection compared to vaccination alone (22). Similarly, Altarawneh et al. reported that hybrid immunity conferred superior protection against symptomatic Omicron infection, reinforcing its relevance in the context of viral evolution and immune escape (20).

Importantly, hybrid immunity is not merely additive—it reflects a synergistic enhancement of immune memory and functional responsiveness. Evidence from immunological studies further supports this concept. Turner et al. demonstrated that mRNA vaccines administered after infection sustain germinal center activity and promote the formation of long-lived plasma cells, thereby supporting durable antibody production and long-term humoral immunity (18).

VACCINE PLATFORMS AND IMMUNE MECHANISMS

COVID-19 vaccine platforms are strategically designed to activate protective immunity by engaging both humoral and cellular components of the adaptive immune system. Each platform—mRNA, DNA, viral vector, inactivated virus, live attenuated virus, and recombinant protein—employs a distinct mechanism to present the SARS-CoV-2 spike (S) protein or its immunogenic domains to host cells. For instance, mRNA vaccines such as Pfizer-BioNTech and Moderna utilize host cellular machinery to synthesize the spike protein intracellularly, thereby inducing robust $CD4^+$ and $CD8^+$ T cell responses alongside high titers of neutralizing antibodies (23). DNA vaccines follow a similar pathway but rely on plasmid-based transcription, offering greater molecular stability and cost-efficiency, albeit with relatively lower immunogenicity (24).

Viral vector vaccines—including AstraZeneca and Johnson & Johnson—deliver spike protein genes via non-replicating adenoviruses, eliciting strong cellular immunity. However, their efficacy may be influenced by pre-existing vector immunity and rare adverse events such as vaccine-induced thrombotic thrombocytopenia (25). In contrast, inactivated virus vaccines like CoronaVac and BBIBP-CorV expose the immune system to the entire virus particle, offering a favorable safety profile and ease of storage, though they often require adjuvants and booster doses due to lower immunogenicity. Live attenuated vaccines, such as COVI-VAC and MV-014-212, mimic natural infection and induce both mucosal and systemic immunity, yet demand stringent biosafety controls due to the potential for uncontrolled replication. Recombinant protein vaccines—including Novavax and UB-612—deliver purified spike or receptor-binding domain (RBD) proteins with adjuvants, primarily stimulating B cell-mediated antibody responses and $CD4^+$ T cell activation (18).

These platform-specific characteristics are summarized in Table I, which provides a comparative overview of immunological mechanisms, strengths, limitations, and variant-specific effectiveness (26-31). For example, mRNA vaccines demonstrate 60–70% effectiveness against Delta and Omicron following booster administration, while inactivated vaccines show variable efficacy (50–78%) but maintain strong protection against severe disease and mortality (29). Viral vector vaccines such as Sputnik V and J&J report efficacy ranging from 72% to 91.6%, though performance may decline in regions with high-transmissibility variants (28). Recombinant protein platforms offer up to 96% efficacy with excellent $CD4^+$ T cell activation (31), and live attenuated candidates show promising broad protection, although clinical data remain limited (30).

VACCINE SAFETY AND REACTOGENICITY IN AT-RISK POPULATIONS

The safety profile of COVID-19 vaccines in individuals with allergic predispositions and chronic respiratory conditions warrants careful consideration, given their immunological sensitivity and potential for adverse reactions. Among the most serious concerns is the risk of anaphylaxis, a rapid-onset, potentially life-threatening hypersensitivity reaction. Although rare, anaphylaxis has been reported following administration of mRNA vaccines, primarily attributed to excipients such as PEG, which is used to stabilize lipid nanoparticles in both Pfizer-BioNTech and Moderna formulations (5). PEG hypersensitivity, while uncommon, may be underdiagnosed, and individuals with prior reactions to PEG-containing therapeutics or cosmetics should be screened prior to vaccination. The Centers for Disease Control and Prevention (CDC) recommends that vaccination sites be equipped with trained personnel and emergency supplies, including epinephrine, to manage such reactions promptly. Recent pharmacovigilance analyses have further substantiated these risks, with Boufidou et al. reporting that although anaphylaxis remains exceedingly rare, it is disproportionately observed in individuals with known excipient sensitivities (32).

In respiratory populations—particularly those with asthma, chronic obstructive pulmonary disease (COPD), or eosinophilic bronchitis—post-vaccination reactogenicity may manifest as transient exacerbation of airway symptoms. These include increased cough, wheezing, or shortness of breath, which may be misinterpreted as vaccine-related complications but often reflect underlying disease ac-

Table I: Comparative analysis of COVID-19 vaccine platforms.

Vaccine Platform	Immunological Mechanism	Advantages	Limitations	Effectiveness Against Variants
mRNA (Pfizer, Moderna)	Host cells synthesize spike protein → activation of T cells and antibody production	Rapid development, high immunogenicity, safe, non-live virus.	Requires cold-chain storage, common local and systemic reactions.	Effective against Delta and Omicron with booster (60–70%) (26).
DNA (ZyCoV-D, INO-4800)	Plasmid DNA transcription → mRNA → spike protein → adaptive immune activation.	High stability, cost-effective, capable of encoding multiple antigens.	Lower transcription efficiency, weaker immune response compared to mRNA.	Primary efficacy 66.6%, 100% protection against moderate disease (27).
Viral Vector (AZ, J&J)	Adenoviral vector delivers spike gene → antigen expression → activation of T and B cells.	Fast production, strong T cell response.	Pre-existing vector immunity, rare risk of VITT (thrombosis).	Sputnik V: 91.6%, J&J: 72% (US), lower in regions with high-transmissibility variants (28).
Inactivated Virus (CoronaVac, BBIBP-CorV)	Whole inactivated virus exposure → humoral and cellular immune activation	Safe, suitable for vulnerable populations, easy to store	Lower immunogenicity, requires adjuvants and boosters	Efficacy varies: 50–78%, strong protection against severe disease and mortality (29).
Live Attenuated Virus (COVI-VAC, MV-014-212)	Limited replication of live virus → immune response mimicking natural infection	High immunogenicity, induces mucosal immunity	Risk of uncontrolled replication, requires strict biosafety controls	High efficacy across disease severity, data still limited (30).
Recombinant Protein (Novavax, UB-612)	Administration of spike or RBD protein → B and T cell activation via adjuvants	Stable, safe, suitable for global distribution	Complex manufacturing, lower RBD-specific response	Efficacy 69.5–96%, strong antibody and $CD4^+$ T cell responses (31).

mRNA: messenger Ribonucleic Acid, **DNA:** Deoxyribonucleic Acid, **AZ:** AstraZeneca, J&J: Johnson & Johnson, **VITT:** Vaccine-Induced Immune Thrombotic Thrombocytopenia, **RBD:** Receptor Binding Domain, **$CD4^+$ T cell:** Cluster of Differentiation 4 Positive T cell, **BBIBP-CorV:** Beijing Institute of Biological Products COVID-19 Vaccine, **COVI-VAC:** Live attenuated intranasal COVID-19 vaccine candidate, **MV-014-212:** Live attenuated intranasal vaccine candidate (Meissa Vaccines), **UB-612:** Multitope protein/peptide-based COVID-19 vaccine candidate.

tivity or immune activation. Importantly, current evidence suggests that the benefits of vaccination in these groups far outweigh the risks, with significant reductions in COVID-19-related hospitalization and mortality observed among vaccinated individuals with respiratory comorbidities (3). This trend is further supported by stratified outcome data presented in Table II, which highlights the markedly lower incidence of severe COVID-19 among vaccinated individuals with chronic respiratory conditions, as well as the importance of tailored post-vaccination monitoring for patients with prior respiratory exacerbations (33-38).

Pharmacovigilance data from global surveillance systems such as VAERS (United States) and EudraVigilance (Europe) have provided valuable insights into adverse event profiles across vaccine platforms. These data indicate that most adverse events in at-risk populations are mild to moderate, including injection site pain, fatigue, and low-grade fever, with serious events remaining exceedingly rare (32). Continuous monitoring and transparent reporting remain essential to ensure public trust and to refine clinical guidelines for vulnerable groups. Personalized vaccination strategies—including extended observation periods, premedication protocols, and interdisciplinary coordination—can further mitigate risks and enhance safety outcomes in allergic and respiratory populations, as emphasized by Montin et al. in their recommendations for individualized vaccine administration protocols (4).

VACCINE EFFICACY AND IMMUNE DURABILITY

Seroconversion Rates and Antibody Titers in Respiratory Patients

Seroconversion following COVID-19 vaccination in individuals with chronic respiratory diseases—such as

Table II: Vaccine safety and reactogenicity in at-risk populations.

Study	Population Focus	Vaccine Type(s)	Key Findings	Implications for At-Risk Groups
Werner et al. (33)	General population incl. comorbidities	mRNA (Moderna), Viral Vector (ChAdOx1)	ChAdOx1 had highest rate of systemic reactions (85.3%), mRNA-1273 had highest rate of local reactions (73.9%)	Individuals with respiratory conditions may experience transient symptoms, PEG-related hypersensitivity should be screened
San Francisco Ramos et al. (34)	Booster recipients incl. elderly and comorbid	mRNA, Viral Vector, Inactivated, Protein Subunit	mRNA vaccines most reactogenic, inactivated vaccines least, full-dose > half-dose, heterologous boosters more reactogenic	Booster choice should consider reactogenicity profile, especially in allergic or immunocompromised patients
Mathioudakis et al. (35)	Real-world recipients incl. respiratory patients	Mixed platforms	Prior COVID-19 infection increased risk of breathlessness (RR 2.05), flu-like illness, and fever	Respiratory patients may benefit from pre-vaccination counseling and post-dose monitoring for airway symptoms
Chalkias et al. (36)	Adults receiving 5th dose (XBB.1.5 booster)	mRNA-1273.815 (monovalent), mRNA-1273.231 (bivalent)	Reactogenicity similar to prior mRNA vaccines, robust neutralizing antibody responses against JN.1 and EG.5.1	Updated mRNA boosters are well tolerated and immunogenic, including in previously vaccinated individuals with comorbidities
Romantowski et al. (37)	European population (EudraVigilance data)	Comirnaty, Spikevax, Vaxzevria, Janssen, Novavax, Valneva	Serious allergic reaction rates per 100,000 doses: Comirnaty (1.53), Spikevax (2.16), Vaxzevria (88.6), most common: edema and anaphylaxis	Confirms overall safety, excipient-specific screening (PEG, polysorbate) recommended for allergy-prone individuals
Warkentin et al. (38)	17,269 recipients in Germany incl. comorbidities	mRNA, Viral Vector (homologous & heterologous regimens)	mRNA-1273 most reactogenic, ChAdOx1 least local reactions, medical consultations rare across all regimens	Supports safe use in respiratory and allergic populations, booster reactogenicity manageable with proper counseling

mRNA: messenger Ribonucleic Acid, **DNA:** Deoxyribonucleic Acid, **PEG:** Polyethylene Glycol, **RR:** Relative Risk, **ChAdOx1:** Chimpanzee Adenovirus Oxford 1 (AstraZeneca viral vector vaccine), **mRNA-1273:** Moderna COVID-19 vaccine, **mRNA-1273.815 / mRNA-1273.231:** Updated Moderna monovalent and bivalent boosters, **XBB.1.5, JN.1, EG.5.1:** SARS-CoV-2 Omicron subvariants, **Comirnaty:** Pfizer-BioNTech COVID-19 vaccine, **Spikevax:** Moderna COVID-19 vaccine, **Vaxzevria:** AstraZeneca COVID-19 vaccine, **Janssen:** Johnson & Johnson COVID-19 vaccine, **Novavax:** Protein subunit COVID-19 vaccine (NVX-CoV2373), **Valneva:** Inactivated whole-virus COVID-19 vaccine, **EudraVigilance:** European Union drug safety monitoring system.

asthma, COPD, and lung cancer—has shown variable outcomes, often influenced by underlying inflammation, immunosuppressive therapy, and smoking status. Studies indicate that while most respiratory patients do mount a detectable humoral response, peak antibody titers tend to be lower and decline more rapidly compared to healthy controls (39). For example, lung cancer patients demonstrated sufficient seroconversion six weeks post-vaccination, but antibody levels dropped significantly by 24 weeks, particularly among active smokers. A systematic review by Harboe et al. further confirms that mRNA-based vaccines elicit higher neutralizing antibody titers than viral vector or inactivated platforms, with homologous mRNA regimens offering superior immunogenicity in patients with chronic pulmonary diseases (3). These findings underscore the need for tailored vaccination schedules and post-vaccination monitoring in respiratory populations.

T Cell Memory and Cross-Variant Protection

Beyond humoral immunity, T cell-mediated responses play a critical role in long-term protection against SARS-CoV-2, especially in the context of emerging variants. T cell memory induced by vaccination has been shown to be broad and durable, targeting multiple viral epitopes and

maintaining cross-reactivity even against immune-evasive strains such as Omicron (40). Importantly, T cell responses are less affected by mutations in the spike protein, allowing for sustained protection against severe disease despite waning antibody levels. Research from the Dutch National Institute for Public Health demonstrates that heterologous vaccine regimens can enhance T cell breadth, while age and CMV seropositivity may modulate responsiveness (41). These insights support the integration of cellular immunity metrics into vaccine efficacy assessments, particularly for vulnerable groups with impaired humoral responses.

Booster Response and Waning Immunity

Booster doses have proven essential in restoring and prolonging immune protection, particularly as vaccine-induced immunity wanes over time. Meta-analyses reveal that vaccine effectiveness against symptomatic Omicron infection drops below 20% within six months of the primary series, and less than 30% nine months post-booster (42). However, booster administration significantly extends the half-life of anti-spike IgG antibodies, with studies showing a 71–84% increase in durability compared to the primary series (43). Notably, individuals with asthma exhibited stronger and more sustained humoral responses post-booster, suggesting that certain respiratory phenotypes may benefit disproportionately. These findings reinforce the importance of timely booster campaigns and adaptive dosing strategies to maintain population-level immunity and reduce breakthrough infections.

SPECIAL CONSIDERATIONS FOR PEDIATRIC AND ELDERLY SUBGROUPS

Age-Related Immune Modulation in Allergic and Respiratory Conditions

Age is a critical determinant of immune responsiveness, particularly in individuals with allergic or respiratory comorbidities. In pediatric populations, the immune system is still maturing, often characterized by Th2-skewed responses that predispose to allergic sensitization and asthma. Conversely, elderly individuals experience immunosenescence—a progressive decline in both innate and adaptive immunity—marked by reduced naïve T cell output, diminished B cell diversity, and chronic low-grade inflammation ("inflammaging"). These age-related shifts influence vaccine efficacy and tolerability. For instance, while neutralizing antibody titers may remain stable across age groups, Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity (ADCC) decline significantly in older adults, compromising viral clearance and long-term protection (44). Tailored vaccine formulations, including adjuvanted platforms and high-antigen content regimens, have shown promise in overcoming these age-specific immunological barriers (45).

Pediatric Asthma and Vaccine Tolerability

Children with asthma represent a unique subgroup in COVID-19 vaccination strategies due to their heightened airway reactivity and variable immune profiles. Current evidence suggests that COVID-19 vaccines are generally well tolerated in pediatric asthma populations, with no significant increase in adverse events compared to non-asthmatic peers. A narrative review by Grandinetti et al. found that vaccine-induced immunogenicity was robust across asthma severity levels, and that controlled asthma did not predispose to vaccine-related exacerbations. However, children with uncontrolled asthma may be at increased risk of severe COVID-19 outcomes, reinforcing the importance of timely vaccination (46). Parent-reported data also indicate a decline in symptomatic asthma prevalence following widespread vaccination and public health measures, suggesting indirect benefits from reduced viral exposure and improved disease management (47). Clinical protocols should emphasize asthma control prior to vaccination and include extended observation for children with prior hypersensitivity reactions (46, 47).

Geriatric COPD and Immunosenescence

In elderly patients with chronic obstructive pulmonary disease (COPD), vaccine responsiveness is shaped by both disease-related inflammation and age-associated immune decline. Immunosenescence in this group is characterized by impaired antigen presentation, reduced T cell proliferation, and diminished antibody production, all of which compromise vaccine-induced protection (48). Studies show that while mRNA vaccines elicit adequate humoral responses in older adults, the durability and breadth of protection are often reduced, necessitating booster strategies and adjuvanted formulations. COPD itself exacerbates systemic inflammation and oxidative stress, further impairing immune fitness. Villar-Álvarez et al. advocate for integrated vaccination schedules that include COVID-19, influenza, pneumococcal, and herpes zoster vaccines to mitigate cumulative respiratory risk (49). Lifestyle interventions—such as smoking cessation, nutritional

support, and physical activity—can also enhance immune resilience and improve vaccine outcomes in this vulnerable population (48, 49).

FUTURE DIRECTIONS AND RESEARCH GAPS

Although COVID-19 vaccine development has achieved unprecedented speed and scale, several critical gaps remain—particularly in addressing the needs of individuals with allergic predispositions and chronic respiratory conditions. As the pandemic continues to evolve, future research must move beyond generalized efficacy metrics and adopt more personalized, adaptive, and interdisciplinary approaches (4).

One emerging priority is the expansion of stratified immunogenicity studies that evaluate vaccine responses across clinically diverse subgroups. Patients with asthma, COPD, autoimmune diseases, or malignancies often exhibit altered humoral and cellular immunity due to chronic inflammation or immunosuppressive therapy. Harboe et al. demonstrated that individuals with chronic pulmonary diseases had significantly lower antibody titers and faster waning compared to healthy controls, especially among corticosteroid users and active smokers (3). These findings underscore the importance of tailoring vaccine schedules and monitoring strategies to individual risk profiles. A structured overview of this and other strategic directions is presented in Table III (3,49-52).

In addition to stratification, the development of mucosal vaccines and variant-adapted formulations offers a promising avenue for enhancing protection at the site of viral entry. Lavelle and Ward emphasized that intranasal platforms can elicit robust mucosal IgA responses and tissue-resident T cell immunity—both critical for preventing early infection and transmission (50). Afkhami et al. further demonstrated that mucosal delivery of next-generation vaccines provided broad protection against both ancestral and variant strains, including Omicron (51). These innovations, while promising, require rigorous evaluation of formulation stability, delivery mechanisms, and cross-variant efficacy before widespread implementation (50, 51).

Equally important is the integration of allergy and pulmonology expertise into vaccine policy and clinical workflows. Individuals with prior anaphylaxis, uncontrolled asthma, or eosinophilic disorders often face uncertainty regarding vaccine safety, contributing to hesitancy and

Table III: Comparative overview of future directions and research gaps in COVID-19 vaccination

Aspect	Stratified Immunogenicity Studies	Mucosal Vaccines & Variant-Adapted Formulations	Integration of Allergy & Pulmonology in Vaccine Policy
Primary Objective	To understand immune responses based on comorbidities, age, and immunomodulatory therapy	To enhance local protection and adapt to viral mutations	To ensure safety and efficacy of vaccination in high-risk populations
Target Population	Patients with asthma, COPD, autoimmune diseases, lung cancer, or severe allergies	Individuals at high risk of transmission and reinfection	Patients with a history of anaphylaxis or respiratory exacerbations
Required Data	Antibody profiles, T cell memory, impact of immunosuppressive therapy	Mucosal efficacy, cross-variant protection, local immune durability	Allergy history, disease control status, vaccine response metrics
Advantages	Supports personalized vaccine schedules and booster planning	Potential to prevent early infection in the upper respiratory tract	Enhances public trust and vaccination adherence
Research Challenges	Patient and treatment heterogeneity	Formulation stability, novel administration routes (e.g., inhalation, intranasal)	Fragmentation between clinical specialties and public health policy
Representative Studies	Harboe et al. (3)	Lavelle & Ward (50), Afkhami et al., (51)	Lyons et al. (52), Villar-Álvarez et al. (49).
Clinical Implications	Adjustment of vaccine dose, interval, and platform selection	Development of second-generation vaccines with greater flexibility	Implementation of allergy screening protocols and extended post-vaccination observation

COPD: Chronic Obstructive Pulmonary Disease, **T cell:** T lymphocyte.

under-vaccination. Lyons et al. reported that structured allergy screening and individualized vaccine protocols enabled safe immunization in high-risk patients without serious adverse events (52). Villar-Álvarez et al. highlighted the importance of aligning vaccination schedules with immune fitness in elderly COPD patients, advocating for multidisciplinary coordination across specialties to ensure safe and equitable access (49).

Taken together, these future directions—stratified immunogenicity, mucosal innovation, and interdisciplinary integration—represent a roadmap for refining COVID-19 vaccination strategies in the face of ongoing epidemiological and immunological complexity. By addressing these gaps, researchers and clinicians can enhance clinical outcomes and reinforce public confidence in immunization programs.

CONCLUSION

COVID-19 vaccination has demonstrated remarkable efficacy in reducing disease burden globally, yet critical gaps remain in its application among individuals with allergic and respiratory conditions. This manuscript highlights the need for stratified immunogenicity studies, the promise of mucosal and variant-adapted vaccine platforms, and the importance of integrating allergy and pulmonology expertise into vaccination policy. By synthesizing immunological mechanisms and clinical considerations, the study underscores the urgency of developing inclusive, adaptive, and evidence-based strategies that reflect the complexity of real-world populations. These insights are particularly relevant for international stakeholders seeking to optimize vaccine safety, equity, and effectiveness across diverse clinical settings.

Acknowledgement

The authors sincerely express their gratitude to Fis Citra Ariyanto for her valuable contribution as a translator. In addition, the authors report that an artificial intelligence tool, Copilot version 5.1 (developed by Microsoft Corporation), was used during manuscript preparation to assist with language editing, sentence refinement, and enhancement of academic narrative clarity. The use of this tool was limited to technical support and did not contribute to the formulation of scientific concepts, data interpretation, analysis of results, or the drawing of conclusions. Full responsibility for the scientific content and academic integrity of this work rests entirely with the authors.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this study.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

Concept: **Hamidia Maulaningtyas,** Design: **Resti Yudhawati, Alfian Nur Rosyid,** Data collection or processing: **Hamidia Maulaningtyas,** Analysis or Interpretation: **Hamidia Maulaningtyas, Resti Yudhawati, Alfian Nur Rosyid,** Literature search: **Hamidia Maulaningtyas,** Writing: **Hamidia Maulaningtyas, Resti Yudhawati,** Approval: **Hamidia Maulaningtyas, Resti Yudhawati, Alfian Nur Rosyid.**

REFERENCES

1. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 2021;184(4):861-880.
2. Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol 2021;21(8):475-484.
3. Harboe ZB, Hamm SR, Pérez-Alós L, Sivapalan P, Priemé H, Wilcke T, et al. Antibody responses and risk factors associated with impaired immunological outcomes following two doses of BNT162b2 COVID-19 vaccination in patients with chronic pulmonary diseases. BMJ Open Respir Res 2022;9(1):e001268.
4. Montin D, Santilli V, Beni A, Costagliola G, Martire B, Mastrototaro MF, et al. Towards personalized vaccines. Front Immunol 2024;15:1436108.
5. Kuehn BM. Rare PEG allergy triggered postvaccination anaphylaxis. JAMA 2021;325(19):1931.
6. Qin SX, Cheng FWT, Kwok WC, Fung LWY, Ma TT, Yiu HHE, et al. Effectiveness and respiratory adverse events following inactivated and mRNA COVID-19 vaccines in patients with COPD and asthma: a Chinese population-based study. Drug Safety 2024;47(2):135-46.
7. Hill J, Montross D, Ivarsson M. Diversity and inclusion in clinical trials: Evolution throughout the development of an mRNA COVID-19 vaccine. Front Public Health 2023;11:1113003.
8. Pepperrell T, Rodgers F, Tandon P, Sarsfield K, Pugh-Jones M, Rashid T, et al. Making a COVID-19 vaccine that works for everyone: ensuring equity and inclusivity in clinical trials. Glob Health Action 2021;14(1):1892309.
9. Sinuraya RK, Nuwarda RF, Postma MJ, Suwantika AA. Vaccine hesitancy and equity: lessons learned from the past and how they affect the COVID-19 countermeasure in Indonesia. Glob Health 2024;20(1):11.
10. Matuchansky C. Protection against SARS-CoV-2 after vaccination and previous infection. N Engl J Med 2022;386(26):2534.
11. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat Immunol 2015;16(4):343-353.
12. Pulendran B, P SA, O'Hagan DT. Emerging concepts in the science of vaccine adjuvants. Nat Rev Drug Discov 2021;20(6):454-475.

13. Teijaro JR. Cytokine storms in infectious diseases. Semin Immunopathol 2017;39(5):501-503.
14. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol 2020;20(6):375-388.
15. Juno JA, Tan H-X, Lee WS, Reynaldi A, Kelly HG, Wragg K, et al. Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. Nat Med 2020;26(9):1428-1434.
16. Tarke A, Coelho CH, Zhang Z, Dan JM, Yu ED, Methot N, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. Cell 2022;185(5):847-859.e11.
17. Goel RR, Painter MM, Apostolidis SA, Mathew D, Meng W, Rosenfeld AM, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. Science 2021;374(6572):abm0829.
18. Turner JS, O'Halloran JA, Kalaidina E, Kim W, Schmitz AJ, Zhou JQ, et al. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. Nature 2021;596(7870):109-113.
19. Manfrini N, Notarbartolo S, Grifantini R, Pesce E. SARS-CoV-2: A Glance at the innate immune response elicited by infection and vaccination. Antibodies 2024;13(1):13.
20. Altarawneh HN, Chemaitelly H, Ayoub HH, Tang P, Hasan MR, Yassine HM, et al. Effects of previous infection and vaccination on symptomatic Omicron infections. N Engl J Med 2022;387(1):21-34.
21. Cho A, Muecksch F, Schaefer-Babajew D, Wang Z, Finkin S, Gaebler C, et al. Anti-SARS-CoV-2 receptor-binding domain antibody evolution after mRNA vaccination. Nature. 2021;600(7889):517-522.
22. Hall V, Foulkes S, Insalata F, Kirwan P, Saei A, Atti A, et al. Protection against SARS-CoV-2 after Covid-19 vaccination and previous infection. N Engl J Med 2022;386(13):1207-1220.
23. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov 2018;17(4):261-79.
24. Krammer F. SARS-CoV-2 vaccines in development. Nature 2020;586(7830):516-527.
25. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med 2021;384(23):2187-2201.
26. Plumb ID, Feldstein LR, Barkley E, Posner AB, Bregman HS, Hagen MB, et al. Effectiveness of COVID-19 mRNA vaccination in preventing COVID-19-associated hospitalization among adults with previous SARS-CoV-2 infection - United States, June 2021-February 2022. MMWR Morb Mortal Wkly Rep 2022;71(15):549-555.
27. Raman R, Patel KJ, Ranjan K. COVID-19: unmasking emerging SARS-CoV-2 variants, vaccines and therapeutic strategies. Biomolecules 2021;11(7):993.
28. Deng S, Liang H, Chen P, Li Y, Li Z, Fan S, et al. Viral vector vaccine development and application during the COVID-19 pandemic. Microorganisms 2022;10(7):1450.
29. Huang Z, Xu S, Liu J, Wu L, Qiu J, Wang N, et al. Effectiveness of inactivated and Ad5-nCoV COVID-19 vaccines against SARS-CoV-2 Omicron BA. 2 variant infection, severe illness, and death. BMC Med 2022;20(1):400.
30. Okamura S, Ebina H. Could live attenuated vaccines better control COVID-19? Vaccine 2021;39(39):5719-5726.
31. Hager KJ, Pérez Marc G, Gobeil P, Diaz RS, Heizer G, Llapur C, et al. Efficacy and Safety of a Recombinant Plant-Based Adjuvanted Covid-19 Vaccine. The New England journal of medicine 2022;386(22):2084-2096.
32. Boufidou F, Hatziantoniou S, Theodoridou K, Maltezou HC, Vasileiou K, Anastassopoulou C, et al. Anaphylactic Reactions to COVID-19 vaccines: an updated assessment based on pharmacovigilance data. Vaccines 2023;11(3):613.
33. Werner F, Zeschick N, Kühlein T, Steininger P, Überla K, Kaiser I, et al. Patient-reported reactogenicity and safety of COVID-19 vaccinations vs. comparator vaccinations: a comparative observational cohort study. BMC Med 2023;21(1):358.
34. San Francisco Ramos A, Liu Sanchez C, Bovill Rose T, Smith D, Thorn N, Galiza E, et al. Comparing reactogenicity of COVID-19 vaccine boosters: a systematic review and meta-analysis. Expert Rev Vaccines 2024;23(1):266-282.
35. Mathioudakis AG, Ghrew M, Ustianowski A, Ahmad S, Borrow R, Papavasileiou LP, et al. Self-reported real-world safety and reactogenicity of COVID-19 vaccines: a vaccine recipient survey. Life 2021;11(3):249.
36. Chalkias S, McGhee N, Whatley JL, Essink B, Brosz A, Tomassini JE, et al. Interim report of the reactogenicity and immunogenicity of severe acute respiratory syndrome coronavirus 2 XBB–containing vaccines. J Infect Dis 2024;230(2):e279-e286.
37. Romantowski J, Nazar W, Bojahr K, Popiołek I, Niedoszytko M. Analysis of allergy and hypersensitivity reactions to COVID-19 vaccines according to the eudravigilance database. Life 2024;14(6):715.
38. Warkentin L, Werner F, Zeschick N, Kühlein T, Steininger P, Überla K, et al. Reactogenicity and safety of COVID-19 primary immunisation and booster vaccination regimens: a comparative observational cohort study. BMC Med 2023;21(1):218.
39. Trontzas IP, Vathiotis I, Economidou C, Petridou I, Gomatou G, Grammoustianou M, et al. Assessment of seroconversion after SARS-CoV-2 vaccination in patients with lung cancer. Vaccines 2022;10(4):618.
40. Wang L, Nicols A, Turtle L, Richter A, Duncan CJ, Dunachie SJ, et al. T cell immune memory after covid-19 and vaccination. BMJ Med 2023;2(1):e000468.
41. Brummelman J, Suárez-Hernández S, de Rond L, Bogaard-van Maurik M, Molenaar P, van Wijlen E, et al. Distinct T cell responsiveness to different COVID-19 vaccines and cross-reactivity to SARS-CoV-2 variants with age and CMV status. Front Immunol 2024;15:1392477.

42. Menegale F, Manica M, Zardini A, Guzzetta G, Marziano V, d'Andrea V, et al. Evaluation of waning of SARS-CoV-2 vaccine-induced immunity: a systematic review and meta-analysis. JAMA Netw Open 2023;6(5):e2310650.
43. Korosec CS, Dick DW, Moyles IR, Watmough J. SARS-CoV-2 booster vaccine dose significantly extends humoral immune response half-life beyond the primary series. Sci Rep 2024;14(1):8426.
44. Sievers BL, Altaf M, Cheng MTK, Kamelian K, Cormie C, Doffinger R, et al. Age-associated defect in ADCC response to COVID-19 vaccine. NPJ Vaccines 2025;10(1):132.
45. Doherty TM, Weinberger B, Didierlaurent A, Lambert PH. Age-related changes in the immune system and challenges for the development of age-specific vaccines. Ann Med 2025;57(1):2477300.
46. Grandinetti R, Palazzolo E, Rizzo L, Carbone R, Pisi G, Fainardi V, et al. Impact of SARS-CoV-2 infection in children with asthma and impact of COVID-19 vaccination: current evidence and review of the literature. Microorganisms 2023;11(7):1745.
47. Davis MM, Halasyamani LK. COVID-19 vaccination and parent-reported symptomatic child asthma prevalence. JAMA Netw Open 2024;7(7):e2419979.
48. Chen L, Shao C, Li J, Zhu F. Impact of immunosenescence on vaccine immune responses and countermeasures.Vaccines 2024;12(11):1289.
49. Villar-Álvarez F, de la Rosa-Carrillo D, Fariñas-Guerrero F, Jiménez-Ruiz CA. Immunosenescence, immune fitness and vaccination schedule in the adult respiratory patient. Open Respiratory Arch 2022;4(3):100181.
50. Lavelle EC, Ward RW. Mucosal vaccines - fortifying the frontiers. Nat Rev Immunol 2022;22(4):236-250.
51. Afkhami S, D'Agostino MR, Zhang A, Stacey HD, Marzok A, Kang A, et al. Respiratory mucosal delivery of next-generation COVID-19 vaccine provides robust protection against both ancestral and variant strains of SARS-CoV-2. Cell 2022;185(5):896-915.e19.
52. Lyons D, Murray C, Hannigan S, Sui J, Alamin S, Conlon N, et al. Risk stratification through allergy history: single-centre experience of specialized COVID-19 vaccine clinic. Clin Exp Immunol 2022;209(2):182-187.