Recent developments in the immunopathology of COVID-19

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Abstract

There has been an important change in the clinical characteristics and immune profile of COVID-19 patients during the pandemic thanks to the extensive vaccination programs. Here, we highlight recent studies on COVID-19, from the clinical and immunological characteristics to the protective and risk factors for severity and mortality of COVID-19. The efficacy COVID-19 vaccines and potential allergic reactions after administration are also discussed. The occurrence of new variants of concerns such as Omicron BA.2, BA.4 and BA.5 and the global administration of COVID-19 vaccines have changed the clinical scenario of COVID-19. Multisystem inflammatory syndrome in children (MIS-C) has been identified as an important cause of death of children with COVID-19. Perturbations in immunity of T cells, B cells, and mast cells, as well as autoantibodies and metabolic reprogramming may contribute to the long-term symptoms of COVID-19. Atopic diseases, such as allergic asthma and rhinitis, have been shown to be associated with a lower susceptibility and better outcomes of COVID-19. At the beginning of pandemic, EAACI developed guidelines that provided timely information for the management of allergic diseases and preventive measures to reduce transmission in the allergic clinics. The global distribution of COVID-19 vaccines and emerging SARS-CoV-2 variants with reduced pathogenic potential dramatically decreased the morbidity, severity, and mortality of COVID-19. Nevertheless, breakthrough infection remains a challenge for disease control. Hypersensitivity reactions (HSR) to COVID-19 vaccines are low compared to other vaccines, and these were addressed in EAACI statements that provided indications for the management of allergic reactions, including anaphylaxis to COVID-19 vaccines. We have gained a depth knowledge and experience in the over 2 years since the start of the pandemic, and yet a full eradication of SARS-CoV-2 is not on the horizon. Novel strategies are warranted to prevent severe disease in high-risk groups, the development of MIS-C and long COVID.

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by infection with the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), has led to alarming numbers of infections and deaths worldwide since it was firstly reported in December 2019[1]. SARS-CoV-2 belongs to the beta-coronavirus genus and is closely related to SARS-CoV[2]. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) via its spike protein to enter cells[3]. The host serine protease transmembrane protease serine 2 (TMPRSS2) cleaves the spike protein and thus enable cellular membrane fusion[4,5]. The host protease furin cleaves the full-length spike precursor to S1 and S2 peptides[6]. S1 directly binds to neuropilin-1 on the cell surface and may facilitate cell invasion and infectivity of SARS-CoV-2[6,7]. ACE2 and TMPRSS2 are expressed at the

epithelial sites of the lung and skin, whereas other host molecules that may be involved in SARS-CoV-2 invasion such as CD147, cyclophilins, CD26 and related molecules are expressed in both epithelium and immune cells[8]. The global administration of COVID-19 vaccines has dramatically decreased the infection rate, severity and mortality of this disease[9,10]. However, new SARS-CoV-2 variants of concern (VOC) of have emerged that will dampen the protective immunity induced by natural infection and current vaccines and lead to breakthrough infection[11,12].

In this review, we highlight recent studies on the clinical and immunological characteristics of COVID-19 in the context of allergy and asthma. The impact of asthma on the susceptibility and severity of COVID-19 is not fully understood and it is discussed here in further detail. Moreover, recent studies on the immune responses and protective effects of COVID-19 vaccines are summarized. The possible culprit components of the vaccines that can induce an allergic reaction are elaborated, along with appropriate vaccination measures for reducing the risk of anaphylaxis.

clinical AND LABoratory characteristics of COVID-19

Clinical characteristics of COVID-19

The clinical scenarios of COVID-19 are diverse and range from asymptomatic to critical illness and even fatal outcomes[5]. The symptoms of COVID-19 include dry cough, fatigue, fever, myalgia, headache, diarrhea, and even respiratory failure[1]. Olfactory and gustatory dysfunctions have been also identified as distinct symptoms of SARS-CoV-2 infection, especially in the western countries[13]. Thus, the respiratory symptoms of COVID-19 may be confused with those of allergic rhinitis (AR) and the common cold[14]. Skin manifestations of COVID-19 include vesicular, urticarial, and maculopapular eruptions and livedo, necrosis, and other vasculitis forms[15] and are more common among European and North Americans than among Asians[16]. The heterogeneity of COVID-19 warrants the elucidation of the phenotypes and endotypes of COVID-19 that will benefit from precision medicine[17,18]. In addition, persistent symptoms such as fatigue, brain fog, body aches, and loss of smell may persist for months following acute infection and are referred as post-acute COVID-19 syndrome or long-COVID[19,20]. After a 1-year follow-up, most COVID-19 recovered patients regain their physical and functional status, although it remains lower than individuals without infection[21].

Children at all ages appear to be susceptible to SARS-CoV-2 infection, although most of them are asymptomatic or develop mild symptoms[22]. Multisystem inflammatory syndrome in children (MIS-C) has been described in COVID-19 patients with an overall 2% mortality[23]. MIS-C predominantly affects children between 6 and 12 years. Most MIS-C children were critically ill, mostly from shock and/or left ventricular dysfunction, with less severe or no respiratory involvement[24]. Regarding the treatment of MIS-C, intravenous immune globulin (IVIG) plus glucocorticoids was associated with a lower risk of cardiovascular dysfunctions but not the recovery from disease when compared to IVIG treatment alone[25,26].

Laboratory findings of SARS-COV-2 infection

The nucleic acid amplification test using RT-qPCR has become the gold standard for detection of SARS-CoV-2. Novel methods have been reported to enhance its efficacy and sensitivity[27]. IgG antibody assays against the receptor binding domain (RBD) and S1 domain were developed as an alternative diagnostic test, albeit with varying accuracies depending on the assay used[28]. Overall, antibody tests for SARS-COV-2 have high specificity but relatively lower sensitivity, which varied with different immunoassays and epitopes[29]. Antigen testing is inexpensive, can provide results in a few minutes and be performed at home. Population-wide antigen testing was demonstrated to reduce the transmission of SARS-CoV-2[30]. Asymptomatic SARS-CoV-2 infection is associated with a longer duration of viral shedding and needs to be promptly detected to stop viral transmission[31,32]. The concentrations of neutrophil extracellular traps increase in the plasma, trachea aspirate and lung autopsies and contribute to the pathophysiology of COVID-19[33,34]. Thus, blood neutrophil extracellular traps can be a potential biomarker for SASR-CoV-2 infection. In addition, asymptomatic patients have lower levels of SARS-COV-2 specific IgG antibodies, which decay during the early convalescent phase[31]. Laboratory changes during COVID-19 have been reviewed and are summarized in our previous studies[35,36].

Risk and protective factors for susceptibility, severity and mortality of COVID-19

Protective factors

Health systems resilience is critical for the control of the COVID-19 pandemic[37]. A healthy diet and sufficient nutrition have been identified as protective factors against SARS-CoV-2 infection[35]. Both the incidence rate and mortality of COVID-19 were lower in Bacillus Calmette-Guerin (BCG)-vaccinated countries than in those without vaccination program[38,39]. Moreover, BCG vaccination during early childhood seems to selectively protect against infection in the elderly[40]. BCG was suggested to enhance innate immune responses, leading to "trained immunity" and confer protection against viral infections[41]. Similarly, recent administration of the mumps-measles-rubella vaccine was observed to be associated with a reduction in SARS-CoV-2 infection in males[42] and severity of COVID-19[43], although the real correlation between this vaccine and COVID-19 is still unclear[44].

Lower levels of nasal ACE2[45] and airway cathepsin L/CTSL1[46], a protease that cleaves and primes the SARS-CoV-2 spike protein, may contribute to the mild disease of COVID-19 in children. Atopy and type 2 inflammation have been associated with a decreased expression of ACE2 in airway epithelial cells and thus lower susceptibility to SARS-CoV-2[47]. More importantly, the type 2 cytokine IL-13 reduced ACE2 expression[47], intracellular viral load and cell-to-cell transmission, whilst increasing the cilial keratan sulfate coating in airway epithelial cells, suggesting a role of IL-13 in attenuating viral shedding and thus reducing the entry, replication, and spread of SARS-CoV-2[48]. Genetic variation of allergic disease was associated with a lower risk of COVID-19[49].

Most studies suggested that AR and chronic rhinosinusitis (CRS) are not associated with a higher risk of susceptibility and severity of COVID-19[35,50,51]. Reduced ACE2 expression was observed in bronchial epithelial cells from patients with concomitant AR and allergic asthma[47], suggesting a potential protective effect of atopy against susceptibility and severity of COVID-19. The expression of ACE2 in nasal polyp tissues of patients with CRS was lower than that of healthy controls[52]. The expression of ACE2 and TMPRSS2 was also lower in the olfactory mucosa of patients with chronic rhinosinusitis with nasal polys (CRSwNP) compared to healthy controls, and the protein expression of ACE2 was negatively correlated with eosinophils numbers in olfactory mucosa[53]. Moreover, the expression of ACE2 was upregulated by interferon (IFN)-γ and downregulated by type 2 cytokines in nasal epithelial cells[47,54,55]. All these data support a protective role of type 2 inflammation against SARS-CoV-2 infection and severe disease.

The corticosteroid dexamethasone can increase ventilator-free days[56] and reduce the death rate[57]in severe and critically ill COVID-19 patients. Mechanistically, dexamethasone treatment restrains neutrophil pathogenicity by reducing IFN^{active}-neutrophils and expanding immunosuppressive immature neutrophils[58]. Treatment with inhaled corticosteroids (ICS) reduced the expression of ACE2 in induced sputum[59] from asthma patients and in bronchial epithelia from patients with chronic obstructive pulmonary diseases[60]. Clinical studies reported that inhaled budesonide in COVID-19 patients reduced time to recovery and resulted in less severe outcome[61,62]. Mechanistically, early Th2 inflammation and attenuated IFN-γ production in the nose may indicate worse clinical outcomes, and ICS budesonide treatment inhibited Th2 inflammation in the nose[63]. Inhalable SARS-CoV-2-specific siRNA and human ACE2-containing nanocatchers were shown to reduce SARS-CoV-2 infection[64,65] and lung inflammation[64], as shown in SARS-CoV-2 infected mice.

Risk factors

The emergence of new variants of SARS-CoV-2, such as Omicron and its subvariants, present a challenge for the eradication of COVID-19 as they have evolved immune escape from the neutralizing antibodies developed in previous infections and vaccinations[66,67]. COVID-19 breakthrough infection has become a major concern associated with the new variants[68]. Whole genome sequencing revealed two distinct mechanisms that can predispose an individual to life-threatening COVID-19, namely failure to control viral replication or an enhanced tendency towards pulmonary inflammation and intravascular coagulation[69]. Older age, male sex, cardiovascular and metabolic comorbidities, racial/ethnic disparities, chronic kidney diseases and cancer have been identified as risk factors for SARS-CoV-2 infection and worse outcomes of COVID-19[35,36].

Healthcare workers are at higher risk of SARS-CoV-2 infection compared to non-healthcare workers[36,70]. Blood levels of neutrophil elastase[71] and histone-DNA[72] were associated with severe and systemic and multi-organ manifestations of COVID-19. Higher levels of bacteria DNA in the system circulation were associated with severe and fatal COVID-19[73]. COVID-19 patients with inborn errors of immunity, except type I IFN immunity errors, exhibit an almost similar natural COVID-19 course compared to the general population[74]. Interestingly, individuals with blood group A are at higher risk of SARS-CoV-2 infection and severe disease, whereas blood group O may be protective against COVID-19[75].

The higher expression of entry receptors ACE2 and TMPRSS2 increase the susceptibility to SARS-CoV-2 infection[35]. Smoking was associated with higher expression of ACE2, TMPRSS2, FURIN, and BSG in bronchial brushes[8] and represents a risk factor for COVID-19 mortality when not adjusted for chronic respiratory diseases[76].

Air pollution has been shown to be associated with SARS-CoV-2 infection and COVID-19 mortality[77]. Mechanistically, air pollutants such as nitrogen dioxide, ozone, and particulate matters (PM) may disrupt the airway epithelial barrier and impair the defense against respiratory viruses[77,78]. The airway epithelial barrier interacts with the respiratory microbiome to shape the immune response in the lungs[79]. In addition, air pollution may contribute to chronic systemic inflammation and a higher prevalence of comorbidities such as cardiovascular and respiratory diseases which have been demonstrated to be risk factors for severe COVID-19[78,80,81]. Air pollution is also correlated with a higher expression of ACE2 receptor in the lung[82]. Furthermore, fine particulate matters such as $PM_{2.5}$ and PM_{10} may act as carriers of SARS-CoV-2 and promote the transmission of this virus[80]. Lockdown during COVID-19 was associated with a reduction in $PM_{2.5}$ concentrations due to reduced traffic emission[83]. Interestingly, the concentrations of airborne pollen correlated with the infection rates of SARAS-CoV-2 in thirty-one countries across both hemispheres[84]. This may be attributed to the impairment of innate antiviral immunity of airway epithelia upon pollen exposure[84].

As an interesting risk factor, exposure to pollution and gut barrier leakiness have been proposed to play a role on COVID-19 severity. Although further studies are needed, severity and excess death rate in northern Italy were suggested to have a link with increased air pollution[78], in accordance with several other studies[85-87].

New variants of concerns

New variants of SARS-CoV-2 emerged sequentially, becoming the predominant strains during the pandemic. These variants have distinct ACE2 binding affinity, virulence, transmissibility and host immune responses[88-100] (Figure 1). Currently, the most pronounced risk factor for SARS-CoV-2 infection is the emergence of new variants or subvariants that are resistant to neutralizing antibodies and with higher transmissibility[101]. The subvariants BA.4 and BA.5, most likely stem from Omicron lineage BA.2[101], were firstly detected in South Africa[99] and are now spreading in Europe and the United States[102]. BA.4 and BA.5 have become the dominant VOC in many European countries. The hospitalization and death rate of BA.4 and BA.5 were significantly lower compared to previous waves of infection in South Africa[99], which may be due to the high population immunity. However, in Portugal, the hospitalization and mortality caused by BA.4/5 were similar to that in the first wave of Omicron infection, which may be due to the higher proportion of elderly individuals in this country[101]. BA.4 and BA.5 carry additional mutations in the spike proteins assisting the immune escape induced by 3-dose vaccinations and by post-vaccination infection of BA.1[103,104]. The Omicron variant is continuously evolving escape antibody neutralization resulting in breakthrough infection of SARS-CoV-2 in both vaccinated and in previously infected individuals[105]. The biological and clinical characteristics of rhinovirus, influenza A, SARS-CoV-2 variants delta, Omicron BA.1 and BA.5 are compared in Table 1.

Table 1. Biological and clinical characteristics and comparison of SAR-CoV2 variants, rhinovirus and influenza.

	Rhinovirus	**Influenza A**	**SARS-CoV-2 Delta B.1.617.2**	**SARS-CoV-2 Omicron B.1.1.529**	**SARS-CoV-2 Omicron BA.5**
Classification	Picornaviridae > Enterovirus > Rhinovirus A/80 subtypes Rhinovirus B/32 subtypes Rhinovirus C/57 subtypes	Orthomyxoviridae > Alphainfluenzavirus > Influenza A virus	Coronaviridae > Orthocoronavirinae > Betacoronavirus > Sarbecovirus > SARS-CoV-2	Coronaviridae > Orthocoronavirinae > Betacoronavirus > Sarbecovirus > SARS-CoV-2	Coronaviridae > Orthocoronavirinae > Betacoronavirus > Sarbecovirus > SARS-CoV-2
Genome	ssRNA positive strand linear	ssRNA negative strand segments	ssRNA positive strand linear	ssRNA positive strand linear	ssRNA positive strand linear
Size	Rhinovirus A 6.5-7.2 kb Rhinovirus B 6.9-7.3 kb Rhinovirus C 6.7-7.2 kb	13.1-13.6 kb	29.8 kb	29.6 kb	29.6 kb
Receptor	Rhinovirus A: Immunoglobulin-type cell adhesion molecule (ICAM-1) B: low-density lipoprotein receptor (LDLR) C: Cadherin-related family and member-3 (CDHR3)	Sialic acid (NeuAc alpha 2,3Gal and NeuAc alpha 2,6Gal) DC-SIGN, L-SIGN	Angiotensin converting enzyme 2 (ACE2)	Angiotensin converting enzyme 2 (ACE2)	Angiotensin converting enzyme 2 (ACE2)
Incubation period	2-3 days	2-5 days	4-7 days	2-4 days	2-4 days

	Rhinovirus	Influenza A	SARS-CoV-2 Delta B.1.617.2	SARS-CoV-2 Omicron B.1.1.529	SARS-CoV-2 Omicron BA.5
Local diseases	Rhinovirus A/B: Common cold, acute otitis media, rhinosinusitis. Rhinovirus C: Lower respiratory tract infections, bronchiolitis and pneumonia, wheezing and asthma exacerbations, croup	Pneumonia, headache, chills, dry cough, fever, myalgia, fatigue, anorexia, nasal congestion, rhinorrhea, sneezing, conjunctivitis	Fever and chills, cough, shortness of breath/dyspnea, burnout, myalgia, headache, loss of taste or smell, sore throat, nasal congestion, runny nose, nausea, vomiting, diarrhea	Runny nose, headache, fatigue, hoarseness, sneezing, sore throat, fever, cough, loss of smell or taste	Runny nose, headache, fatigue, hoarseness, sneezing, sore throat, fever, cough, loss of smell or taste
System diseases		Viremia, myocarditis, myositis, central nervous system symptoms (irritability, lethargy, noise, confusion, encephalopathy, encephalitis, etc.), toxic shock syndrome, cytokine storm, kidney failure, liver failure	Viremia, myocarditis, myositis, central nervous system symptoms (irritability, lethargy, noise, confusion, encephalopathy, encephalitis, etc.), toxic shock syndrome, cytokine storm, kidney failure, liver failure	More focused to elderly and risk groups, same type of diseases as in delta. Relatively low prevalence compared to delta	More focused to elderly and risk groups, same type of diseases as in delta. Relatively low prevalence compared to delta
Risk groups	Babies and toddlers, chronic disease Primary and secondary immunodeficiencies	Older age, chronic diseases (asthma, coronary artery disease, diabetes, cirrhosis, chronic kidney failure, Parkinson's disease, etc.)	Adults 70 years and older, chronic heart disease, diabetes, obesity, immunodeficiency transplantation, cancer chemotherapy, chronic kidney disease, pregnancy	Adults 70 years and older, chronic heart disease, diabetes, obesity, immunodeficiency transplantation, cancer chemotherapy, chronic kidney disease, pregnancy	Adults 70 years and older, chronic heart disease, diabetes, obesity, immunodeficiency transplantation, cancer chemotherapy, chronic kidney disease, pregnancy

	Rhinovirus	Influenza A	SARS-CoV-2 Delta B.1.617.2	SARS-CoV-2 Omicron B.1.1.529	SARS-CoV-2 Omicron BA.5
Mortality	0.001%	0.1%	2-4%	0.01%	Similar to the Omicron BA.1 wave

COVID-19 and asthma

Observational studies indicated a potential protective factor of asthma for the morbidity and mortality of COVID-19[1,50], although conflicting data from the United States and United Kingdom (UK) suggested a higher prevalence of asthma in COVID-19 patients[106]. A UK study found that asthmatic patients were associated with a higher risk of COVID-19[107]. For allergic asthma, the protective effects have been partly attributed to the antiviral effect of eosinophils[35], whose beneficial effects on COVID-19 outcomes depend on ICS[108]. However, whether COVID-19 patients with asthma are at higher risk of long-COVID symptoms is still unclear as there are contradictory research studies[109,110].

It remains unclear whether asthma is a risk factor for the severe and worse outcome of COVID-19. However, it appears to be related to the asthma phenotype, treatment and severity[111,112]. Asthma was shown to be associated with an increased hospitalization risk of COVID-19 both in adults[50] and in children[113]. Another study observed an increased hospitalization rate only in asthmatic patients needing regular ICS or regular/intermittent ICS with add-on therapy[107]. The hospitalization rate of allergic asthmatics was 50% lower compared to non-allergic asthmatics[110]. A recent meta-analysis identified preexisting asthma as a risk factor for intensive care unit (ICU) admission among COVID-19 patients[114]. The heterogeneity of asthma endotypes (allergic vs. nonallergic asthma) may underly the different disease course in these studies[35,110]. Eosinopenia was associated with worse outcomes of COVID-19, including longer duration of hospitalization, higher severity and mortality[1,36,110]. Dynamic monitoring of eosinophils counts in addition toother laboratory indices, such as neutrophil-to-lymphocytes ratio lymphocytopenia and D-dimer, may be used as predictive biomarkers of the outcomes of COVID-19[35,36]. Biologicals were associated with lower susceptibility in asthmatic patients[115]. Omalizumab augmented IFN-α production from plasmacytoid dendritic cells[116], which may also contribute to the protecting effects of asthma against COVID-19.

A lower expression of ACE2 in bronchial epithelial or lung tissue was observed in allergic asthmatic patients[106,117,118]. In addition, ICS may decrease the expression of ACE2 and TMPRSS2 in bronchial epithelia of asthmatic patients[59] and thus contribute to lower susceptibility to infection. The current evidence does not indicate an increased risk of long COVID-19 in asthmatic patients, although studies with more patients are warranted[118]. The symptoms of long COVID-19 are summarized in Table 2.

Table 2.Reported symptoms of post-acute COVID-19 syndrome or long COVID-19.

Organs and systems	Symptoms
General status	Fatigue, general asthenia, low fever, dizziness, sweating[119,120]
Neuro-psychiatric system	Headache, insomnia, depression, distress, anxiety, dysphoria, post traumatic stress disorc
Cardiovascular systems	Chest pain, palpitation, elevated HR, diastolic dysfunction, stress cardiomyopathy, chang
Upper respiratory tract	Runny nose, anosmia, sore throat, blocked nose[120,121]
Pulmonary system	Cough, phlegm, hemoptysis, chest tightness, chest pain, shortness of breath, ventilator a
Gastrointestinal system	Abdominal discomfort, diarrhea, constipation, vomiting, loss of appetite[121]
Hepato-biliary system	Nausea, jaundice, transaminase increase[121]
Endocrine and metabolic system	New- onset hyperglycemia and diabetes, diabetic ketoacidosis, subacute thyroiditis[120,122
Genito-urinary system	Proteinuria, haematuria, development of kidney injury, uncontrolled bladder, pollakiuria
Vascular complications	Thromboembolism, bleeding, disseminated intravascular coagulation[19,125]
Reproduction	Male infertility[122]

Organs and systems	Symptoms
Musculoskeletal system	Arthralgia, myalgia, muscle weakness[121,122]
Dermatological complications	Maculopapular exanthem, papulovesicular rash, urticaria, painful red acral purple papule
Others	Conjunctivitis, neck pain[125]

Immune responses and pathogenesis of COVID-19

The immunological pathogenicity of COVID-19 is complex and may be associated with the virulence of SARS-CoV-2 and the lack of the temporal coordination between innate and adaptive immune responsces[126-128]. Other mechanisms such as pre-existing immunity to SARS-CoV-2, super-antigens and autoimmunity have been also suggested to participate in the immune responses to this virus[129]. Adaptive responses to SARS-CoV-2 develop mainly to the spike protein. It is postulated that SARS-CoV-2 RNA is sensed by toll-like receptor (TLR)-3/7/8 and activates innate immune pathways[130,131]. SARS-CoV-2 replication induced a delayed type I IFN response in lung epithelial cells, which is regulated by melanoma differentiation-associated gene 5 (MDA5)[132]. Activation of NLRP3 inflammasomes participates in the pathophysiology of COVID-19 and is associated with the severity of this disease[133]. Type I IFN-mediated antiviral responses and activation of both $CD4^+$Th1 and $CD8^+$ cytotoxic T lymphocytes result in viral clearance in SARS-CoV-2-infected subjects with mild symptoms[134]. Impairment in the number and function of dendritic cells may also lead to dysregulation in innate and adaptive immunity including antiviral response[129,135]. The insufficient antiviral response[136], or autoantibodies against type I IFNs[137,138], combined with the system inflammation induced by a large number of immune cells and resident tissue cells, may contribute to the cytokine storm in severe disease[131].

Virus-specific IgM and IgA can be detected in the acute phase followed by an increase in virus-specific IgG at a later stage of COVID-19[129]. More severe COVID-19 patients were associated with higher anti-RBD IgA and IgG antibody responses when compared to those not hospitalized or asymptomatic. No deaths were reported in patients with higher a IgG antibody index (NT50/IgG$>$ 100)[139]. Dupilumab (anti-IL-4/13 Rα) used in atopic dermatitis (AD) patients with COVID-19 was associated with a lower IgG antibodies response[140]. Poor and delayed anti-SARS-CoV-2 IgM and IgG antibodies responses correlated with poor outcomes of COVID-19 in children[141]. A visible antibody cross-reactivity was reported to infectious bronchitis virus, a non-SARS-CoV infection and chicken aerosol vaccines particularly in highly exposed veterinarians who administered the vaccines. However, this immune cross-reactivity did not show a viral neutralizing activity and focused on non-RBD antibodies, which substantially differ between SARS-CoV-2 and non-SARS-CoVs[142]. Activated inflammatory caspases can induce pyroptosis which may partly contribute to lymphopenia in COVID-19, and the caspases inhibitors have been suggested to be potential therapeutics for severe and long COVID-19[143].

Mild COVID-19 patients exhibited SARS-CoV-2-specific memory B and T cells responses that display hallmarks of antiviral immunity[144]. The antigen-driven activation of anti-SARS-CoV-2 memory B cells persisted and matured up to 6 months after SARS-CoV-2 infection and may provide long-term protection[145]. Long COVID-19 patients were characterized with over-activated innate immune cells, lacked naive T and B cells and showed persistent elevated expression of IFN-β and IFN-λ1 at 8 months after infection[146]. Mast cell activation may also contribute to long-term COVID-19 as evidenced by persistent mediators release[147]. Diverse autoantibody responses were identified in COVID-19 patients and were correlated with disease severity and duration of hospitalization [138]. Preexisting and de novo autoantibodies were more frequently detected in hospitalized or severe COVID-19 patients and may play a role in post-acute sequelae of COVID-19[148]. Dysregulated respiratory $CD8^+$ T cell responses were associated with impaired lung function after acute COVID-19[149]. In summary, poor viral clearance, persistent inflammation and autoimmunity were proposed as the major mechanisms contributing to long COVID-19[125,131,150,151] (Figure 2).

MANAGEMENT of allergic diseases during THE COVID-19 pandemic

The COVID-19 pandemic has SHAPED the ways medical services are conducted in order to accommodate for the imposed lockdown and social distancing measures. Accordingly, telemedicine was adopted by many physicians to guide the treatment and follow-up of allergic patients[152].

Continuation of intranasal corticosteroids (INCS) was suggested for AR patients with COVID-19 at the recommended doses[153]. Treatment with INCS before SARS-CoV-2 infection was associated with a lower risk of COVID-19-related hospitalization, ICU admission or death[154]. A systematic review assessed the use of INCS on the olfactory dysfunction of COVID-19 patients, but only identified a single study to include in the review[155]. The impact of INCS on the susceptibility and outcomes of COVID-19 is still inconclusive[51]. Oral corticosteroids, biologicals and surgical treatment should be avoided or suspended in CRS patients with SARS-CoV-2 infection[51]. Telemedicine was advocated to replace in-person visits for the care of CRS patients during the COVID-19 pandemic with high patient satisfaction[156].

Inhaled or oral corticosteroids should be continued to for asthmatic patients without SARS-CoV-2 infection to maintain asthma control, and oral corticosteroids and biologicals should be continued to treat severe asthma exacerbations[157]. In the case of asthmatic patients with confirmed SARS-CoV-2 infection, the use of inhalers should be indicated over nebulizers for the delivery of aerosolized medications to avoid viral transmission via aerosol[158]. Current evidence suggests that treatment with biologicals targeting type 2 inflammation does not increase the risk of SARS-CoV-2 infection and COVID-19 severity[159] and may have beneficial effects[115]. Therefore, biologicals may be continued during COVID-19 for asthmatic patients without SARS-CoV-2 infection.

AIT should be temporarily discontinued until recovery for SARS-CoV-2 positive asthmatic patients or in contact with confirmed cases of COVID-19[160]. AIT can be continued in SARS-CoV-2 negative confirmed patients but with a prolonged injection interval[160]. Switching from subcutaneous to sublingual immunotherapy may be considered for AIT during COVID-19[161]. Skin manifestations of COVID-19 may be similar to other viral infections and drug hypersensitivity reactions (DHRs)[162,163]. The diagnosis and management of DHRs induced by medications repurposed and off-label for the treatment of COVID-19 have been discussed in a few review papers[162-164].

Pulmonary function tests such as spirometry should be restricted to those patients with high clinical priority and using a high-efficiency inline filter. The patients should be encouraged to perform peak expiratory flow measurement at home to reduce the possible transmission via small droplets and aerosol generated during the pulmonary function test[165,166].

Many studies have focused on the impact of the COVID-19 pandemic on the status and control of allergic diseases. In asthmatic children, environmental changes, altered medical practice and medication use, changes in transportation and travel patterns, school attendance and physical activity impacted asthma control during the pandemic[167]. A survey revealed that the majority of the AD patients experienced AD flares with mild worsening of the disease during the COVID-19 pandemic[168]. Dupilumab seems to be safe and crucial for a better outcome of COVID-19 and should be continued in AD patients during the COVID-19 pandemic[169]. During COVID-19, AIT was initiated and continued by most physicians in patients without indications of SARS-CoV-2 infection[170]. In contrast, lockdown during COVID-19 resulted in decreased numbers of patients initiating AIT but without significant impact on sublingual immunotherapy[171].

COVID-19 was reported to increase the incidence of acute urticaria[172] and disease activity of chronic urticaria in males but not females, which may be associated with loss of omalizumab efficacy[173]. Single-cell sequencing and proteomic analysis revealed that the cytokine storm associated with severe COVID-19 may promote the activation of monocytes/macrophages and cytotoxic $CD8^+$ T cells, which may be involved in the development of maculopapular drug rash associated with COVID-19[174].

COVID-19 vaccines

Natural SARS-CoV-2 infection does not establish a strong antibody response that can prevent reinfection[175]. COVID-19 vaccines offer promising protective immunity against SARS-CoV-2 infection. Two groups of

vaccines are available for the global vaccination strategy of COVID-19. The classic group includes subunit, inactivated, live-attenuated and virus-like particle vaccines; novel approaches include RNA-based vaccines which deliver RNA coding target viral proteins into human cells[176]. Two mRNA -based vaccines, BNT162b2 and Moderna mRNA vaccines were approved with emergency use or conditioned marked authorization by the USA, European Union and other countries' governmental agencies. Phase III clinical trials and real-world data suggested that COVID-19 vaccines have dramatically reduced severe COVID-19 cases[177] and excess mortality due to COVID-19 (Figure 3), although breakthrough infection in fully vaccinated individuals is not uncommon[178].

Efficacy and immune responses of COVID-19 vaccines

The RBD of the SARS-CoV-2 spike protein is the primary target for neutralizing antibodies induced by COVID-19 vaccines. Specific IgG antibodies against conformational but not sequential RBD epitopes have the potential to block the binding of SARS-CoV-2 with ACE2 and confer protective immunity[179]. Mutations in RBD, as identified in several VOC, display increased binding affinity to ACE2[180] and/or reduced neutralization ability of sera from convalescent and BNT162B2 vaccinated individuals[181-184]. Noticeably, BNT162b2-induced IgG antibodies had higher avidity to mutated RBD than those induced by natural infection[66]. The variant Omicron exhibited approximately fourfold greater immune escape relative to the Beta variant[183]. Prior COVID-19 was associated with higher neutralization capacity for the ancestral virus after BNT162b2 vaccination[183]. More importantly, two doses of mRNA COVID-19 vaccines provided almost non-existent, whereas a booster dose yielded almost 75% protection against symptomatic infection of Omicron[184]. It is predicted that BNT162b2 boosted, or vaccination (two doses) combined with previous infection can prevent 73% symptomatic infection by Omicron, which is significantly higher than in individuals with BNT162b2 vaccination only[183].

Other types of vaccines have also been administered around the world. CVnCoV is a vaccine based on unmodified RNA and induced only a 48% reduction in the incidence of symptomatic disease[185]. CV2CoV is the second-generation unmodified mRNA vaccine but with optimized non-coding regions and enhanced antigen expression. Compared to CVnCoV, CV2CoV induced higher titers of binding and neutralizing antibodies against SARS-COV-2 variants, and memory B and T cell responses non-human primates[186]. The inactivated Sinopharm/BBIBP COVID-19 vaccine is widely used in developing countries including China due to its low storage requirements. Seroconversion rates in unexposed individuals after first and second dose reached 40% and 100% respectively, and younger individuals and women had the highest antibody concentrations. Previous SARS-CoV-2 infection was associated with a strong antibody response after a single dose of the BBIBP vaccine. A sharp increase in antibody concentrations was observed following SARS-CoV-2 infection after the first and second doses[187]. Virus-like particle-based COVID-19 vaccines induced high levels of neutralizing antibodies and protection against infection with SARS-CoV-2 and its variants in mice and rhesus macaques[188,189]. PreS-RBD vaccine was developed based on a recombinant fusion protein consisting of the human hepatitis B virus-derived PreS antigen and two SARS-CoV-2 RBD domains. It induced a robust anti-RBD IgG response in rabbits consisting of an early IgG1 and sustained IgG4 which can be detected in serum and mucosa secretions. Moreover, the vaccine-induced antibodies potently inhibited the interaction of RBD with ACE2 and possessed the neutralizing ability of the omicron VOC[190]. The efficacy and immune responses elicited by different types of COVID-19 vaccines are listed in Table 3.

Table 3. Efficacy and immune response of different SARS-CoV-2 vaccines

Vaccine name	Types of vaccines	Efficacy and immune responses

Vaccine name	Types of vaccines	Efficacy and immune responses

BNT162b2	mRNA vaccines	95% effective in preventing COVID-19 Induced IgG antibodies had higher avidity to mutated RBD than those induced by natural infection[66,183,191]
Moderna	mRNA vaccines	94.1% efficacy at preventing COVID-19 Preclinical testing in advanced clinical evaluation has shown a Th1-skewed vaccine response and no pathologic lung infiltrates[192-194]
AZD1222	Viral vector	After the second dose, efficacy was higher in those with a longer prime-boost interval (vaccine efficacy 81.3% at [?]12 weeks) than in those with a short interval (vaccine efficacy 55.1% at <6 weeks) Higher binding and neutralizing antibody titers in sera with a longer prime-boost interval[195]
Sputnik V	Viral vector	91.6% efficacious against COVID-19 (from day 21 after the first dose, to the day of receiving the second dose) RBD-specific IgG was detected in 98% of samples, with a geometric mean titer (GMT) of 8996, and a seroconversion rate of 98.25% Increased SARS-CoV-2 neutralizing antibody titers By day 28 after the first vaccination, all vaccinated participants had significantly higher levels of IFN-γ secretion upon antigen restimulation compared with the day of administration of the first dose[196]

Vaccine name	Types of vaccines	Efficacy and immune responses
Ad26.COV2.S	Viral vector	The level of protection for the combined endpoints of moderate and severe disease varied: 72% in the United States; 66% in Latin American countries; and 57% in South Africa, 28 days post-vaccination. The investigated vaccine was reportedly 85% effective in preventing severe/critical COVID-19 across all geographical regions. Induced durable protection at low doses in preclinical SARS-CoV-2 challenge studies; initial clinical data showed that a single dose at 5×10^{10} viral particles was safe and induced excellent humoral and cellular immune responses[197-200]
BBIBP COVID-19 vaccine	Inactivated vaccines	Sinopharm has announced an efficacy of 79% A sharp increase in antibody concentrations was observed following SARS-CoV-2 infection after the first and second doses[177,187,201]
Covaxin (BBV152)	Viral vector	81% interim efficacy in preventing COVID-19 in those without prior infection after the 2nd dose In the phase 1 trial, BBV152 induced high neutralizing antibody responses that remained elevated at 3 months after the 2nd vaccination In the phase 2 trial, BBV152 enhanced humoral and cell-mediated immune responses compared with the phase 1 trial[202]

Vaccine name	**Types of vaccines**	**Efficacy and immune responses**
CoronaVac	Inactivated virus	Multiple studies in different countries: 50.7% (Brazil), 56.5% (Chile), 65% (Indonesia), 78% (Brazil) and 91% (Turkey) Immune responses in phase 2 were much better than those recorded in phase 1; seroconversion rates over 90% in both the 3 μg and 6 μg groups Well tolerated and induced humoral responses against SARS-CoV-2 In an exploratory analysis by age, seroconversion rates at day 28 after the second dose were higher than 94% in the 3 μg and 6 μg groups for participants aged 60-64 years, 65-69 years, and 70 years or older, with GMTs ranging from 36.4 to 55.2[201,203,204]
AD5-nCOV	Viral vector	Tolerable and immunogenic in healthy adults. Specific humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination, and rapid, specific T-cell responses were noted from day 14 after one shot of the vaccine Aerosolized Ad5-nCoV is well tolerated, and two doses of aerosolised Ad5-nCoV elicited neutralizing antibody responses, similar to one dose of intramuscular injection. An aerosolized booster vaccination at 28 days after first intramuscular injection induced strong IgG and neutralizing antibody responses[205,206]
CV2CoV	Unmodified RNA vaccines	Induced higher titers of binding and neutralizing antibodies against SARS-COV-2 variants, and memory B and T cell responses non-human primates[186].

Vaccine name	Types of vaccines	Efficacy and immune responses
PreS-RBD vaccine	Recombinant fusion protein	Median inhibitions of RBD to ACE2 (100 ng RBD: 8.6% to 98.3% inhibition, median inhibition: 16.0%; 50 ng RBD: 14.4% to 99.4% inhibition, median inhibition: 52.8%) Robust anti-RBD IgG response in rabbits consisting of an early IgG1 and sustained IgG4 which can be detected in serum and mucosa secretions The vaccine-induced antibodies potently inhibited the interaction of RBD with ACE2 and possessed the neutralizing ability to the omicron VOC[190].
NVX-CoV2373	Protein subunit	A two-dose regimen of the NVX-CoV2373 vaccine administered to adult participants conferred 89.7% protection against SARS-CoV-2 infection and showed high efficacy against the B.1.1.7 variant Elicited immune responses that exceeded levels in COVID-19 convalescent serum[207,208]

Allergic reactions to COVID-19 vaccines

Local and systemic reactions were reported in phase III clinical trial of the ChAdOx1 nCoV-19 vaccine, which were mostly mild and moderate in intensity[209]. Cutaneous adverse effects of the available COVID-19 vaccines include injection site reactions, urticaria, angioedema, exacerbation of atopic eczema and systemic allergic reactions including anaphylaxis[210]. Anaphylaxis to the BNT162b2 vaccine was reported several days after the initiation of public vaccinations[211]. Overall, the incidence of COVID-19 mRNA vaccine-associated anaphylaxis is very low[212], with only was 4.8 per million doses for BNT162b2 and 5.1 per million doses for mRNA-1273 according to data from Vaccine Safety Datalink[213]. Moreover, the second dose of the BNT162b2 vaccine elicited a higher rate of systemic events[191]. Nevertheless, the incidence of anaphylaxis- associated with COVID-19 vaccines is comparable to that of other vaccines[214] and the benefits may outweigh the potential risks of COVID-19 vaccinations[215,216]. Unfortunately, the fear of an allergic reaction has caused vaccine hesitancy in the general public, haltering global vaccination efforts[217].

Polyethylene glycol (PEG) is an additive present in the Pfizer-BioNtech and Moderna mRNA vaccines used to prevent premature degradation of the nanoparticless[218], and it has been suggested to be the major culprit for anaphylaxis to COVID-19 vaccines[219]. PEG and its derivatives are also widely used in household products including toothpaste, cosmetics, pharmaceuticals, and foods[220]. Many types of vaccines, therapeutic medications and diagnostic media contain PEG with different molecular weights and their risks of anaphylaxis has been previously reported[220,221]. Exposure to products containing PEG via intravenous and intramuscular injection is the major route causing HSR to PEG. There is evidence showing that lipid-conjugated PEG or PEGylated liposomes have a stronger immunogenicity than PEG alone and may contribute to the anaphylaxis elicited by COVID-19 mRNA vaccines[222,223]. Anti-PEG IgE-mediated HSR, complement

activation-related pseudoallergy induced by anti-PEG IgM and IgG antibodies and potential interaction of PEG with mast cells and viral RNA have been suggested to underly COVID-19 vaccine anaphylaxis[222,224]. IgG and IgM antibodies against PEG were found in up to 25% of the population without known prior exposure to PEGylated products and in up to 89% of patients with known prior exposure to PEGylated products[225]. Other excipients than PEG present in authorized COVID-19 vaccines might also cause severe allergic reactions to COVID-19 vaccines and need appropriate allergological assessment[226].

EAACI has reported recommendations to perform in vivo tests (skin prick test and intradermal test) and in vitro tests (basophil activation test, BAT) to the vaccines or their components in individuals with severe reactions to the first dose of COVID-19 vaccines[227]. The positive rate of skin test with PEG or mRNA vaccine in patients with reactions to COVID-19 mRNA vaccine or with previous PEG or polysorbate allergies was very low[228,229]. Thus, the clinical significance of skin testing with mRNA vaccine in those with negative skin testing results with PEG is still unknown. BAT performed in patients with PEG allergy demonstrated that BNT162b2 and AZD1222 vaccines and PEGylated lipids, but not unmodified PEG, can activate mast cells[223]. Thus, positive BAT results to mRNA vaccines may be a potential diagnostic tool for confirming HSR to PEG excipient.

Studies have shown that most individuals with allergic reactions to the first dose tolerated well the second dose irrespective of the skin test results[230,231]. Thus, the second dose vaccine may be administered after careful evaluation and under careful monitoring in an allergy clinic. In a position paper by EAACI, allergic patients without prior allergic reaction to any of the vaccine components and patients with mild and moderate allergies were recommended that they should not be excluded from COVID-19 vaccinations[227]. On the contrary, it would put population immunity with vaccination at risk due to the high prevalence of allergic diseases[227] . However, anaphylaxis may occur after vaccination in the absence of a history of allergic disease. Therefore, strategies for the prevention, diagnosis and treatment of severe allergic reactions and a list of recommended medications and equipment for vaccine centers were provided in the EAACI statement to minimize the risk of allergic reactions to COVID-19 vaccines[227]. Anaphylaxis induced by COVID-19 vaccines is rare but may be more severe in older people due to comorbidities and polypharmacy[232]. Intramuscular injection of adrenaline remains the first-line therapy for anaphylaxis in older people[232]. Modified dosing or alternative vaccines were recommended by EAACI for those with confirmed reactions to COVID-19 vaccines[227]. Herein, we provide a flow chart for the treatment of allergic reactions to COVID-19 vaccines (Figure 4).

Perspectives and conclusions

Anthropogenic activities, climate change and global population movement set a perfect environment for new outbreaks of zoonotic pathogens. Using the knowledge and experience gained from the COVID-19 pandemic, there is an urgent need to develop novel strategies to predict and prevent the emergence and transmission of novel pathogens [233]. Effective surveillance of new SARS-CoV-2 variants and reporting their transmissibility and rate of breakthrough infection is warranted to assist international policymaking[234]. The trajectory of COVID-19 needs to be closely monitored to further our understanding of the immunity waning, antigen drifting and re-entries from zoonotic reservoirs [235]. As we deepen our knowledge on COVID-19, vaccination strategies should be updated and revised, such as frequent administration of booster doses. The continuously mutating virus warrants the development of novel vaccines targeting current variant sequences[236]. The impacts of COVID-19 on allergen sensitization and the incidence of allergic disease are still unknown and need to be investigated by the society of allergy and clinical immunology.

In conclusion, similarly to other respiratory viruses, full eradication of COVID-19 is not on the horizon. Novel strategies should be developed for the prevention and management of this disease, particularly for patients at high risk of severe disease and to prevent MIS-C and long COVID. The emergence of new variants of concerns and global vaccinations efforts have substantially changed the clinical and immunological profiles of COVID-19.

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YG and CA initiated the idea and designed the study. HZ, YS, YW, DY, DA, IO, AKA, ZY, XC, AZ, JH, GL contributed to the data collection and writing. HZ and YG finalized the manuscript. MA and CA revised the manuscript. All authors contributed to the final review.

FIGURE LEGENDS

Figure 1. Daily new cases and deaths, and the characteristics of different mutations in the COVID-19 coronavirus pandemic. The data were obtained from*https://www.worldometers.info/coronavirus/*

Figure 2. Proposed mechanisms of long COVID-19. Persistent tissue damage and inflammation are suggested to be the major mechanisms of persistent symptoms of COVID-19. Persistent dendritic cell (DC) deficiency, autoimmunity and dysbiosis may also contribute to the long-term symptoms. Severe disease, aging and female are risk factors for long COVID-19.

Figure 3. Time-series visualization of global daily reported COVID-19 deaths, excess mortality estimates and vaccinations. Source data were downloaded from Our World in Data on August 19, 2022. Excess mortality estimates and the 95% confidence interval (CI) were modeled by the Economist. The lines indicate 7-day rolling averages of daily reported deaths and excess mortality estimates per million people as well as all daily vaccination doses per billion people, including boosters that are counted individually.

Figure 4. Flow chart for the management of individuals with allergic reactions to COVID-19 vaccines. Premedication can be used for those with local reactions before the next dose of vaccine. For those with systemic symptoms, assessment with skin test or basophil activation test (BAT) in an allergy clinic is recommended and then treated with premedication or alternative vaccines.

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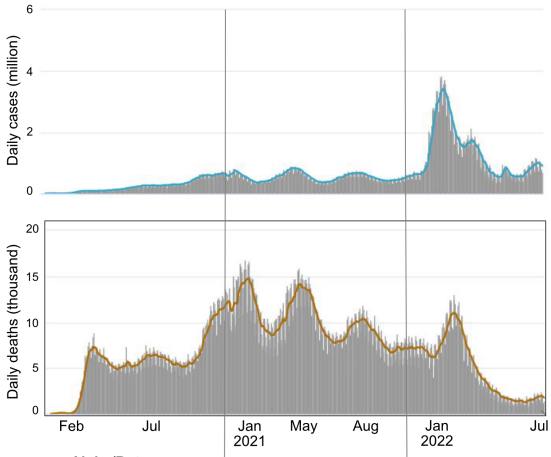
Fig 1



Alpha/Beta

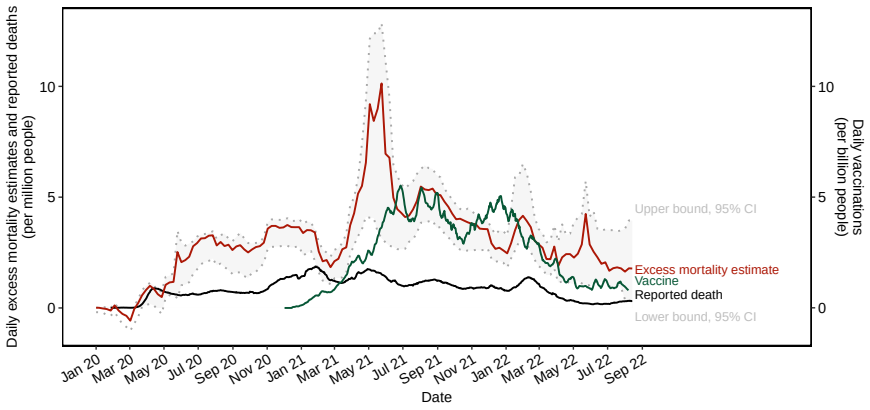
- Compared to Wuhan-Hu-I reference genotype, enhanced binding to ACE2
- Increase transmissibility
- 1.5 to 2 times increased reproduction rate
- Increased virulence

Delta

- Compared to Wuhan-Hu-I reference genotype, higher replication efficiency
- Higher transmissibility
- Reduced sensitivity to host immune response
- Increased virulence

Omicron

- Compared to Wuhan-Hu-I reference genotype, 34 different mutations of BA.1 variant and 32 mutations of BA.4 and BA.5 variants in the spike glycoprotein
- Some of the mutations are predicted to enable immune escape
- Spike protein of Omicron tends to use the alternative cathepsin L mediated entry rather than the canonical TMPRSS2 pathway that improves its ability to infect cells in the upper respiratory tract
- Reduced infection of lower respiratory tract due to lack of TMPRSS2 expressing cells
- Less virulent than Alpha and Delta variants



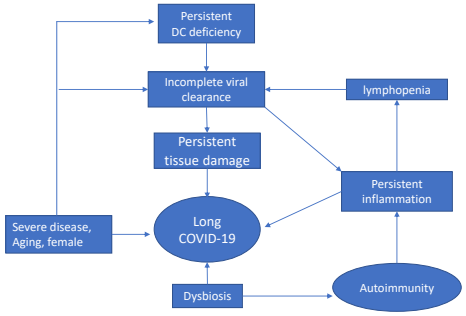


Fig 2

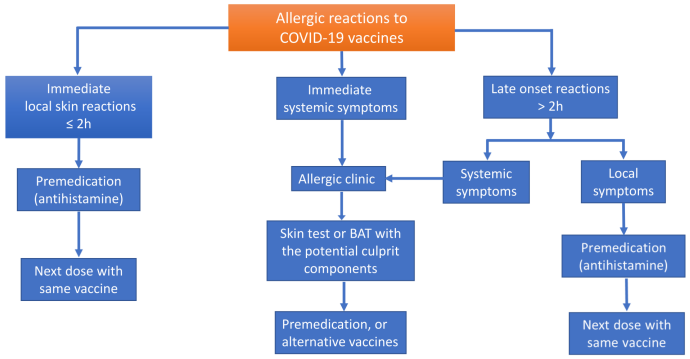


Fig 4