Glossary:

Innate immunity: Genetically predetermined, unspecific and quick immune response, following on the recognition of pathogen- and or danger-associated molecular patterns.

Adaptive immunity: Antigen-specific memory conferred by clonal selection of optimized antigen recognition and subsequent expansion of T and B cells.

Innate trained immunity: Mechanisms depending on metabolic and epigenetic reprogramming in innate cells following first antigenic contact. These cells can mount more efficient immune responses upon subsequent encounter to related or unrelated antigens.

ILC: Innate lymphoid cells can be associated with type 1, 2 or 3 immune response.

Self-antigen: Own proteins and their epitopes recognized by the immune system that do not trigger an immune response and instead are tolerated

Non-self-innocuous antigen: Harmless structures not associated with one self, for which the immune system will be tolerant, as they are part of our environment (e.g. pollens)

Type 1 immunity: Type 1 immunity is mounted against intracellular pathogens like *Mycobacterium tuberculosis* or viruses. ILC1, Th1, NK, NKT, Tc1 cells recognize and kill infected cells and their content, and macrophages and neutrophils ingest the dead cells and kill the pathogens.

Type 2 immunity: Type 2 immunity protects against large protozoan pathogens (helminths), toxins and venoms. It is characterized by ILC2, Th2 and Tc2 cells and involves IgE and effector cells basophils, eosinophils and mast cells.

Type 3 immunity: Type 3 immune responses fight against extracellular bacteria or fungi and are characterized by ILC3, neutrophils and Th17 cells, with IL-17 being the main effector cytokine and the neutrophils the primary effector cells.

AIT: allergen immunotherapy is an immune modulation procedure targeting type 2 immunity

COVID-19 vaccination in patients receiving allergen immunotherapy (AIT) or biologicals – EAACI recommendations

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1. Introduction:

A. The purpose of the EAACI position paper

Immune modulation is a key therapeutic tool for allergic diseases and asthma. It can be achieved in an antigen-specific way via allergen immunotherapy (AIT) or in endotype-driven approach using biologicals that target the major pathways of the type 2 (T2) immune response: IgE, IL-5 and IL-4/IL-13.

COVID-19 vaccine provides an excellent opportunity to tackle the global pandemics and is currently being applied in an accelerated rhythm worldwide. It works as well through immune modulation.

Thus, as there is an obvious interference between these treatment modalities recommendations on how they should be applied in sequence are expected.

The European Academy of Allergy and Clinical Immunology (EAACI) gathered an outstanding expert panel under its Research and Outreach Committee (ROC). This expert panel was called to evaluate the evidence and formulate recommendation on the administration of COVID-19 vaccine in patients with allergic diseases and asthma receiving AIT or biologicals. The panel also formulated recommendations for COVID-19 vaccine in association with biologicals targeting the type 1 or type 3 immune response.

In formulating recommendations, the panel evaluated the mechanisms of COVID-19 infection, of COVID-19 vaccine, of AIT and of biologicals and considered the data published for other anti-infectious vaccines administered concurrently with AIT or biologicals.

B. Immune responses to COVID-19 infection

The immune system protects the host against pathogens while maintaining tolerance against self- and innocuous non-self-antigens. Type 1 immune responses are mounted against intracellular pathogens and are orchestrated by specialized immune cells that recognise, kill and remove the infected host cells. Different groups of immune cells orchestrate Type 2 and Type 3 immune responses to fight against helminths or venoms/toxins and extracellular bacteria or fungi, respectively [1], [2]. Deviation of these immune responses may lead to immune deficiencies, autoimmunity, cancer and allergies.

The secretion of interferons (INFs) is one of the most potent antiviral components of the innate immune response. IFNs work by blocking virus attachment, entry, movement, protein production and genome amplification, virus assembly and exit. IFNs also activate other innate and adaptive immune responses. However, in the case of COVID-19, these responses appear to be weakened or deregulated [3]. SARS-CoV and MERS-CoV viruses can inhibit IFN signalling at various levels [4]. A decreased antiviral response through the inhibition of the IFN pathway, along with an ongoing pro-inflammatory response, presumably increased by viral load, can lead to excessive inflammation and worsening of the disease. In the SARS-CoV animal model, a delayed-type I IFN response resulted in the accumulation of inflammatory monocytes and macrophages, leading to elevated cytokines and chemokines in the lungs, vascular leakage, and an impaired T-cell response.

Monocytes, macrophages, and DCs play a key role in antiviral response by interlinking innate and adaptive immunity. Peripheral activation and accumulation of the activated pro-inflammatory agent monocytes and macrophages in the lungs have become the hallmark of symptomatic SARS-CoV-2 infection [5]. Coronaviruses can induce NLRP3 inflammasome activation in monocytes and macrophages, producing high amounts of pro-inflammatory mediators such as IL-6, GM-CSF, IL-1beta, TNF, CXCL-8 or CCL-3, increased cell death, up to the cytokine storm, or the cytokine release syndrome (CRS) [6]. Neutrophils are the dominant cells infiltrating the lung in severe SARS-CoV-2 infection [7]. During systemic inflammation (CRS), neutrophil activation occurs, which may be associated with the release of extracellular neutrophil traps (NETs). This is a way to entrap pathogens, but on the other hand, NET formation is associated with lung diseases, especially acute respiratory distress syndrome (ARDS). In severe COVID-19 the uncontrolled progressive inflammation likely induces intense cross-talk between NET-releasing neutrophils and macrophage IL-1β secretion, which may lead to further complications [8]. CD8 + T cells directly neutralize infected cells, and CD4 + T cells help B cells initiate a humoral response against the pathogen. T cells play an essential role in developing virus-specific memory CD8

+ and CD4 + T cells [9], [10], [11]. SARS-CoV-2 specific CD8 + and CD4 + T cells have recently been identified in ~ 70% and 100% of patients following COVID-19, respectively. Delayed development of adaptive responses along with prolonged virus clearance has been reported in cases of severe SARS-CoV-2 infection [12]. The mechanisms related to lymphocytopenia are still unknown in SARS-CoV. Moreover, as with SARS-CoV, alteration of antigen-presenting cell (APC) function followed by impairment of T cell stimulation may lead to the ineffective and delayed formation of virus-specific T cells [13], [14], [15]. Data on NK cell counts in COVID-19 patients are variable. Functional depletion of NK cells and CD8+ T cells has been described in relation to severe SARS-CoV-2 infection [16]. The number of Treg cells is reduced during SARS-CoV-2 infection [17]. The intense cytokine response can induce apoptosis of T cells [18].

Infection with human SARS-CoV-2 activates the immune mechanisms of B and T helper cells, with production of neutralising antibodies. The antibody response occurs 4-8 days after the onset of COVID-19 symptoms and is dominated by IgM [19]. This initial IgM response is followed by consecutive IgA and IgG (10-18 days). The development of mucous IgA can prevent re-infection with SARS-CoV-2, while circulatory IgA can contribute to the systemic neutralisation of SARS-CoV-2 and the reduction of inflammation during active infection [20]. SARS-CoV-2 IgG neutralising antibodies specific to the spike (S) protein are detected in the serum 2-3 weeks after infection. Both the extent and quality of the IgG response during the neutralisation of SARS-CoV-2 are critical. For this reason, passive transfer of human serum obtained during convalescence, was suggested as therapeutic approach [21]. However, low affinity or suboptimal levels of IgG may increase viral entry through IgG binding to the Fcγ receptor expressed on immune cells. This mechanism may induce the release of inflammatory cytokines and contribute to the CRS associated with severe COVID-19 [22]. The potential contribution of the B cell population to COVID-19 pathology has not yet been elucidated. The main issue with B-cell resistance to SARS-CoV-2 is the duration of the antibody response (IgG) after the infection and the ability of SARS-CoV-2-specific memory B cells to expand or replenish the plasma cell compartment after re-infection [23](figure 1).

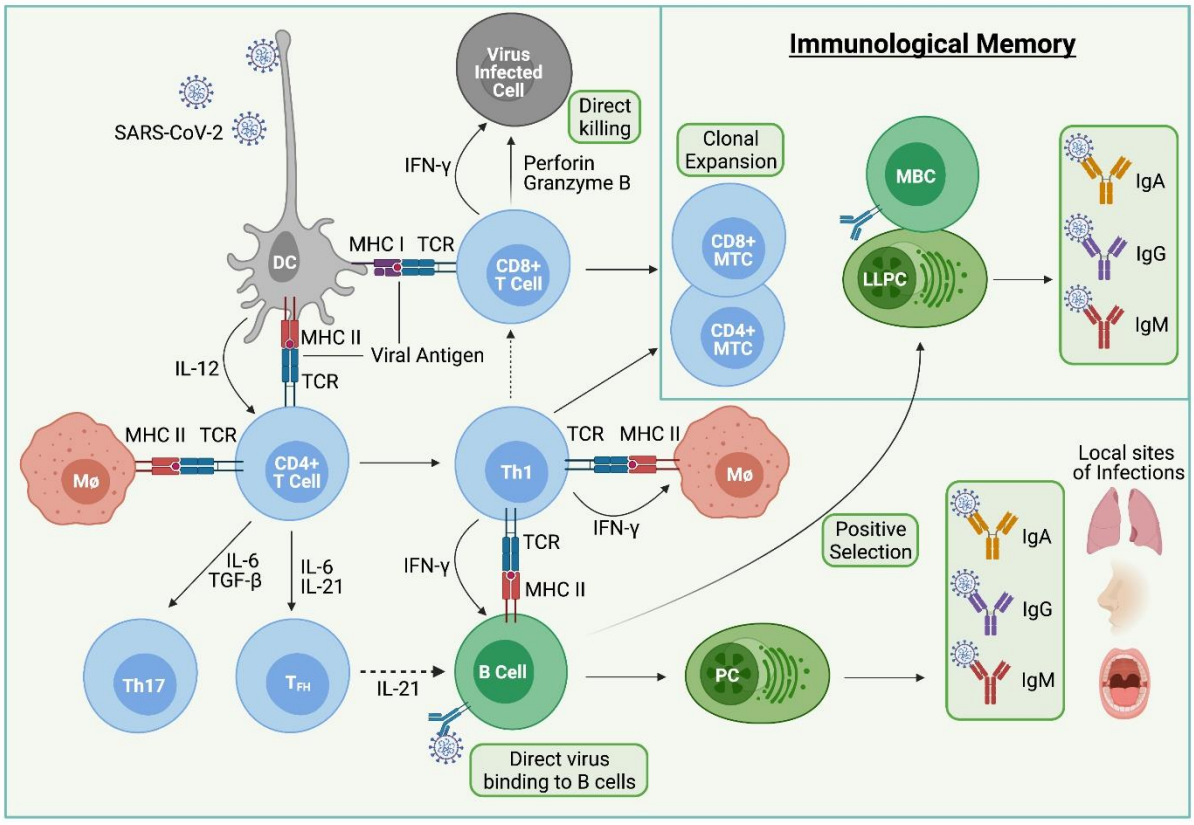

Figure 1. Immune response to SARS-CoV-2.

DC present SARS-CoV-2 derived antigenic peptides on MHC II to CD4+ T cells, in the setting of IL-12. CD4+ T cells differentiate to Th17 in the setting of IL-6 and TGF-β, T_{FH} in the setting of IL-6 and IL-21 and Th1 cells. Moreover, Mφ can also present SARS-CoV-2 derived antigenic peptides on MHC II to activate CD4+ T cells and Th1 cells. DC also present SARS-CoV-2 derived antigenic peptides on MHC I to CD8+ T cells, which in turn become activated and release IFN-y and elicit direct killing of virus infected cells via perforin and granzyme B. CD4+ T cells and CD8+ T cells undergo clonal expansion into CD4+ MTC and CD8+ MTC, constituting immunological memory. T_{FH} cells release IL-21 which induces class switching in B-cells to virus specific IgA, IgG and IgM. Furthermore, SARS-CoV-2 virus can directly bind to B-cells. High affinity B-cells differentiate into PC, which secrete antibodies. Furthermore, positively selected high affinity B cells differentiate into MBC and LLPC secreting IgA, IgG and IgM, also constituting immunological memory. The local sites of infection for SARS-CoV-2 are the lung and the nasal and oral mucosa. DC, Dendritic Cell; MHC, Major Histocompatibility Complex; Th1, T helper Type 1 cell; Ig, immunoglobulin; T_{FH}, T Follicular helper cell; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TGF-β, transforming growth factor β; IFNγ, Interferon-γ; IL, Interleukin; LLPC, Long-lived high affinity plasma cell; MBC, Memory B-cell; Mφ, macrophage; Th17, T helper 17 cell; PC, plasma cell; MTC, memory T cell.

C. Immune mechanisms of COVID-19 vaccination

The major mechanism of protection against viral infection triggered by the licensed vaccines relies on generating a protective antibody responses that persist over time [24]. Persistent antibodies against viruses are generated at microanatomical sites of secondary lymphatic organs called germinal centres (GCs), where antigen-activated B cells generate antibodies with the high-affinity for the pathogen [25]. Only the B cells reaching high affinity are positively selected and saved from apoptosis. This process produces long-lived high-affinity plasma cells (LLPC) and memory B cells (MBC), which are the desired cell types induced by vaccination.

The efficacy of vaccination against SARS-CoV-2 may to a large extent dependent on the induction of T-cell responses for several reasons. Among CD4+ T cells, follicle T helper cells (Tfh) are key regulators of GCs affinity matured antibody responses [26], [27]. Other subsets of CD4+ T cells may serve various essential functions, including facilitating optimal CD8 T cell responses. In addition, cytotoxic CD8+ T cells responsible for the direct killing of pathogen-infected cells by releasing molecules such as granzyme and perforin provide an important "safety net" that has to be created by vaccination in case protective antibodies do not completely control the viral infection [28].

The immune response is induced by SARS-CoV-2 mRNA vaccines administered intramuscularly. Both mRNA-lipid nanoparticle and the locally produced antigen (spike protein) are taken up by antigen-presenting cells (APCs) such as dendritic cells (DCs). The APCs then travel to the lymph nodes, where they activate CD4+ and CD8+ T cells. Stimulation of CD8 T cells can induce the formation of cytotoxic T cells that are capable of killing infected cells directly. Stimulated CD4+ T cells can differentiate into Th1 cells or follicle T helper cells (Tfh). By delivering costimulatory molecules and cytokines to B cells, Tfh cells mediate GC formation and select affinity matured GC B cells, which may further differentiate into LLPC or MBC. Tfh cells may differentiate towards the Th1 or Th2 phenotype, which will affect the switching of antibodies produced by LLPC to Th1- or Th2-dependent antibody class [29].

Specific immune reactions occur during vaccination, depending on the route, dose and type of vaccine and adjuvants. The work on 200 new potential vaccine preparations is underway around the globe. Researchers are currently testing 82 vaccines in clinical trials in humans, and 23 have reached the final phase. At least 77 preclinical vaccines are under active investigation in animal models. The vaccine platform used for specific COVID-19 vaccines include mRNA-based, recombinant viral vectors (Viral vector non-replicating), inactivated vaccine virus, subunit (recombinant protein vaccines), viral-like Proteins (VLP). Live-attenuated, or recombinant viral vectors (Viral vector Replicating).

2. COVID-19 vaccination:

A. RNA-based vaccines

Two RNA-based COVID-19 vaccines have been the first to be approved globally, produced by Pfizer and Moderna [30]. The Pfizer vaccine BNT162b2 is a lipid-nanoparticle formulated nucleoside-modified RNA (modRNA) encoding SARS-Cov-2 full-length spike glycoprotein modified by 2 proline mutations to lock it in the prefusion conformation [31], [32], [33]. The Moderna vaccine mRNA-1273 is also a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the prefusion stabilised full-length spike protein of SARS-CoV-2 [34].

The efficacy of BNT162b2 mRNA COVID-19 Vaccine was evaluated in a multinational, placebo-controlled pivotal phase 2/3 trial with 43,548 participants aged 16 years old or older over the course of two months. Intramuscular administration of 30-µg BNT162b2, 21 days apart compared with placebo, elicited 95% protection against COVID-19 [31],[35]. A case-control study compared 596,618 people who were newly vaccinated in Israel and matched them to unvaccinated controls according to demographic and clinical characteristics. The outcomes were collected from 20 December 2020 to 1 February 2021 in time periods: days 14 to 20 after the first dose of vaccine or day seven or more after the second dose. Two doses of the mRNA vaccine reduced symptomatic cases by 94%, hospitalisation by 87%, and severe COVID-19 by 92%. In Israel, the second dose of vaccine is given on day 21 in line with the trials and the manufacturer's recommendation. The study also suggests the vaccine is effective against the B.1.1.7 variant, which was first identified in the UK. During the study period, this variant was isolated in Israel in up to 80% of cases [36].

The efficacy of the Moderna vaccine was investigated in phase 3 randomised placebo-controlled trial with 30,420 participants (15210 participants in each group) across the United States. Similar to Pfizer vaccine efficacy, the Moderna vaccine also elicited 94.1% protection against symptomatic COVID-19 when injected at 100-µg after the second dose on day 29 [34]. Binding and neutralising antibodies were produced in 33 healthy adult participants in an ongoing phase 1 trial [37], stratified according to age, at 180 days after the second dose of 100 µg (day 209) [38]. Prospective cohorts of health care personnel, first responders, and other essential and frontline workers over 13 weeks in eight U.S. locations confirmed that authorised mRNA COVID-19 vaccines (Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273) are highly effective in real-world conditions [39]. FDA has demonstrated in a retrospective analysis of 31,069 individuals receiving at least one dose of either mRNA-1273 or BNT162b2 vaccine a 88.7% protection against SARS-CoV-2 infection with onset at least 36 days after the first dose. Furthermore, vaccinated patients who were subsequently diagnosed with COVID-19 had significantly lower 14-day hospital admission rates than propensity-matched unvaccinated COVID-19 patients [40].

Phase I and II trials of both Pfizer and Moderna vaccines were shown to induce neutralising antibodies against the spike protein, as well as cellular immune responses. Because viral antigens are recognised by T cells, these cells respond to viruses by producing several protective molecules such as interferon γ (IFN-γ), which is secreted by CD4+ and CD8+ T-cells and their corresponding memory compartment [41].

The mRNA-1273 vaccine was also shown to induce robust binding antibody responses to both full-length S-2P and receptor-binding domain in all participants after the first vaccination in a time- and dose-dependent manner. CD4 T cell responses were elicited at the 25-µg and 100-µg doses. Upon stimulation by S-specific peptide pools, these responses were strongly biased toward the expression of Th1 cytokines with minimal type 2 helper T-cell (Th2) cytokine expression. CD8 T-cell responses to S-2P were detected at low levels after the second vaccination in the 100-µg dose group [42].

Possible escape of a new SARS-Cov-2 variant called B.1.1.7 from BNT162b2-mediated protection was investigated in a study using pseudoviruses bearing SARS-CoV-2-S spike protein variants of either Wuhan reference strain or the B.1.1.7 with sera of 16 participants from a previously reported trial. The immune sera were reported to have equivalent neutralising antibody titres to both variants, emphasising that the new variant will unlikely compromise the efficacy of BNT162b2 [43]. Another preliminary study investigating the immune responses of Moderna's vaccine against the same variant revealed similar reactions to Pfizer's vaccine [44].

B. Recombinant vaccines

Gam-COVID-vac (Sputnik V) is the world's first registered vaccine based on human adenoviral vectors (rAd26 and rAD5) and the world`s first registered vaccine against SARS-CoV-2. The vaccine is administered intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5), both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein. The vaccine's efficacy is confirmed at 91.6% based on the analysis of data from 21,977 volunteers: the vaccine-induced strong humoral and cellular immune responses [45].

ChAdOx1 nCoV-19 vaccine contains DNA delivery within a non-replicating recombinant adenovirus (AdV) system consists of a chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene. The vaccine efficacy is 91%, respectively, based on data from blinded, randomized, controlled trials done across three countries, on 23,848 participants. Effective neutralizing antibodies were induced following prime vaccinations and significantly increased after a booster dose on day 28 [46].

Johnson & Johnson vaccine is a vector vaccine as well (working name Ad.26.COV2.S or JNJ-78436725). It uses the replication-defective human type 26 adenovirus vector expressing SARS-CoV-2 virus S glycoprotein. Previously, the same vector (AdVac® technology) was used in the Ebola vaccine [47].

C. Inactivated vaccines

The inactivated vaccines platform was the first technology used in a plethora of vaccination strategies developed since the beginning of the SARS-CoV-2 pandemic.

Authorized vaccines of this type are the Chinese CoronaVac, BBIBP-CorV, and WIBP-CorV; the Indian Covaxin; and the Russian CoviVac [48], [49], [50], [51].

These vaccines elicit antibody response which target not only the S-protein of the SARS-Cov-2 virus but also other antigens such as virus N proteins. [52], [53].

Compared to vaccines that target only the S-protein of the SARS-Cov-2 virus, inactivated vaccines may benefit from the broader antigenic spectrum of the whole virus resulting in a more heterogenous immune response.

D. Covid-19 subunit vaccinations

Currently, most of the protein subunits vaccines have focussed on the virus's spike protein subunits or the domain directly involved in receptor binding [54]. In contrast with traditional vaccines, subunit vaccines should have fewer side effects and higher safety at the injection site. These vaccines require adjuvant activities to exert an optimal effect because of the poor immunogenicity of the subunit's proteins. Adjuvants are included as vehicles to target antigen-presenting cells or to enhance the innate immune response.

Further vaccine development could aim at structural, non-structural and accessory proteins of SARS-CoV-2 could potentially serve as targets of vaccine-induced immune responses. B-cell and T-cell epitopes are highly conserved between SARS-CoV-2 and SARS-CoV, indicating that a vaccine against such a conserved epitope may elicit cross-immune responses to mutant viruses. Among viral structures, S protein is the main protein used as a target in COVID-19 vaccines. In experimental models, recombinant S trimeric protein mimics the native S form inducing high neutralizing antibodies titres accompanied by high Th1 and low Th2 cell responses that reduce viral loads in lungs and confer clinical protection after the SARS-CoV-2 challenge. The authorized COVID-19 subunit vaccines include peptide preparation EpiVacCORONA and RBD-Dimer [55].

3. Immunological mechanism of allergen immunotherapy and biologicals

A. Allergen immunotherapy

Allergen immunotherapy (AIT) is an intervention for allergic diseases and asthma inducing tolerance to the allergen responsible for eliciting the symptoms [56]. By continuous administration of high amount relevant allergen(s), a tolerogenic immune response is generated. Main mechanisms involve early effector cell desensitization and progressive onset of a regulatory B and T cell response followed by significant decreases in allergen-specific Type 2 especially Th2 cells and Type 2 ILCs in circulation and the affected tissue [57], [58], [59]. Although AIT induced changes are antigen-specific, recent data support a positive effect in the overall rebalance of Th2 skewed innate immune system [60], [61].

COVID-19 does not considerably increase in severity in allergic disease, with conditions such as rhinitis, urticaria, and atopic dermatitis or even asthma, if controlled under background treatment [62], [63]. The immunological mechanisms of AIT and COVID-19 vaccine do not seem to interfere as both primarily target the immune system in a specific, non-overlapping manner.

The effect of AIT on the effector cell desensitization, especially mast cell desensitization is rather limited, antigen/allergen specific and occurrs early during AIT [64]. However, mast cells are not considered to be relevant for antiviral immune response.

B. Biologicals targeting the Type 2 immune response (anti-IgE, anti -IL-4R, IL-5, IL-13, TSLP)

Biologicals block specific players within the cascade of immunological events that result in chronic allergic inflammation and or acute exacerbations. Their availability transformed the way severe allergic diseases are treated beyond systemic steroids or immunosuppressants. Despite their specificity for molecular targets, pathways of allergic inflammation may overlap with immunologic events that serve to cope with viral infections or are associated with vaccine response. Real-life relevance is sometimes difficult to predict due to redundancies within the human immune system.

Up-stream of allergen-specific responses innate cells drive allergic inflammation in tissue and mucosal surfaces. Tezepelumab blocks the epithelial-derived cytokine TSLP and thereby is considered to address upstream events in the tissue/mucosa. TSLP promotes epithelial inflammation and initiates Type 2 dendritic cells, activates ILC2 and adaptive Type 2 T and B-cells. It is considered a central regulator of environmental triggers such as allergens, pollutants and viruses and is upregulated in the airways of asthmatics. The clinical relevance of TSLP blockade via the monoclonal antibody Tezepelumab demonstrated clinical efficacy in treating adults with uncontrolled asthma [65]. During COVID infection, TSLP levels in serum are not altered, neither over time nor in patients with severe disease [66]. Very recent findings demonstrate a suppressive effect of TSLP on recall responses of CD8+ T-cells in the context of infections [67]. Bone marrow-derived cells from TSLP -/- mice display an enhanced viral response in a neonatal rodent model of RSV infection [68]. Despite the lack of human data, blocking TSLP may have beneficial effects in suppressing viral infections, while no information is available on vaccine response under TSLP blockade.

IL-4 and IL-13 receptors share the IL4R alpha chain. Similar to TSLP, IL-13 reduces barrier function, facilitates virus entry and negatively affects rhinovirus induced immune responses. IL-4 is the critical cytokine that promotes the isotype switch direction IgE and is a key cytokine in B-cells function. It also acts on innate APCs and effector cell populations. IL-4 also plays a role in neutrophil function [69]. IL-4 producing CD8+ T cell subsets can dampen the development of effective Th1 immunity in several viral infections, including chronic HIV-1 [70]. Inhibition of IL-13 expression may enhance antiviral immunity [71]. In the context of vaccine immune response, it has been shown that IL-4, IL-4Ra, and IL-13 polymorphisms influence pneumococcal serotype-specific IgG antibody responses [72]. Transient inhibition of IL-4 and or IL-13 at the vaccination site has been shown to induce sustained solid, high-quality CD8+ T cell immunity against a mucosal pathogen such as HIV-1 and IL-4/IL-13 receptors/antagonist have also been proposed as vaccine adjuvants [73].

C. Mechanisms of biologicals targeting the non-Type 2 pathway

Biologicals represent an essential cornerstone in the management of non-Type 2 inflammatory diseases. Anti-cytokine antibodies are applied in patients with inflammatory bowel disease, rheumatic diseases or inflammatory skin diseases [74]. These antibodies modulate cytokine dysregulation being involved in disease onset and progression. In autoimmunity, B-cell depletion via anti-CD20 biological is used in organ specific but also systemic diseases for elimination of auto-reactive B-cells and plasma cells [75]. Moreover, Natalizumab is a humanized anti–α4 integrin monoclonal antibody impeding cell migration by interference of integrin binding to their endothelial receptors. This antibody is used to suppress CNS inflammation in multiple sclerosis patients. Also in oncological patients, immune modulating therapies are applied [76]. Small molecules result in immune-check-point inhibition leading to better tumor defense in a variety of cancers [77]. Besides substantial treatment efficacy, biologicals substantially influence the immune response to microorganisms, often resulting in the enhanced susceptibility to infections.

4. COVID-19 vaccination in patients receiving allergen immunotherapy or biologicals

A. Kinetics of the immune reaction during the COVID-19 vaccine

BNT162b1 and b2 (BioNTech/Pfizer): Vaccine doses are administered intramuscularly on day 0 and 21. Concentrations of RBD-binding IgG and SARS-CoV-2-neutralizing titres were assessed at baseline, 7 and 21 days after the BNT162b1 priming dose, and 7 and 21 days after the boost dose (days 29 and 43). Twenty-one days after the first dose, concentrations of RBD-binding IgG had increased in a dose-dependent manner, ranging from 265 to 1,672 units (U) ml−1, with an increase (21 days after boost) up to in the range of 3,920–18,289 (U) ml−1. SARS-CoV-2 neutralising antibodies increased in a dose-dependent manner 21 days after the priming dose. Substantially higher serum-neutralising titres were achieved seven days after the booster dose. On day 43 (21 days after the boost), the neutralising and RBD-binding start decreasing. The intensity of RBD-specific CD4+ T cell responses correlated positively with both RBD-binding IgG and SARS-CoV-2-neutralizing antibody titres. The intensity of RBD-specific CD8+ T cell responses correlated positively with vaccine-induced CD4+ T cell responses but did not significantly correlate with SARS-CoV-2 neutralising antibody titres. RBD-specific CD4+T cells secreted IFN-γ, IL-2, or both, but in most individuals, they did not secrete IL-4. Similarly, fractions of RBD-specific CD8+ T cells secreted IFN-γ and IL-2. Five vaccinated participants were stimulated ex vivo with overlapping RBD peptides and produced the proinflammatory cytokines TNF, IL-1β and IL-12p70, but neither IL-4 nor IL-5. In summary, these findings indicate that BNT162b1 induces functional and proinflammatory CD4+ and CD8+ T cell responses with detection of IFN-γ, IL-2 and IL-12p70, but not IL-4 or IL-5, which indicates a favourable Th1 profile and the absence of a potentially deleterious Type 2 immune response [78]. With this in mind, antigen-specific T-cell responses were characterised in mice 12 and 28 days after BNT162b vaccine immunisation. A strong IFN-γ producing CD4+ and CD8+ T-cell responses, and a high fraction of CD8+ cells that produced IL-2 were observed. Moreover, 28 days after immunisation with 1-μg BNT162b2, splenocytes revealed high levels of Th1 cytokine production (IL-2 or IFN-γ), along with undetectable levels of the Th2 cytokines IL-4, IL-5 or IL13. In addition, one immunisation with BNT162b2 induced high dose level-dependent receptor-binding domain (RBD)- and S1-binding serum IgG titres. Furthermore, IgG elicited by BNT162b2 revealed a strong binding affinity for the recombinant RBD target antigen [32].

mRNA-1273 (Moderna): Vaccine doses are administered intramuscularly on day 0 and 29. Binding antibodies specific to S-2P protein (anti-spike) together with serum neutralising antibody titres against SARS-CoV-2 were measured on days 1, 29, 43, 57, 209, and 394. The vaccine induced increases in the levels of anti-SARS-CoV-2-spike binding antibodies by 28 days after the first vaccination. Their titer substantially increased by 14 days (day 43) after the second vaccination to peak levels of 189 mg/ml in younger participants and 153 mg/ml in older participants [79]. Neutralising antibodies increased from baseline by 28 days post-vaccination. Fourteen days following the booster (day 43), their level significantly increased to a maximum of 1909 mg/ml at 100 mg mRNA-1273 in younger adults and 1686 mg/ml in older adults. Both antibodies remained elevated in all participants 3 months after the booster vaccination. Serum neutralising antibodies continued to be detected in all the participants on day 119 [80], [81].

Ad26.COV2.S (Janssen/Johnson&Johnson) AdV vaccine: Participants received 1 or 2 intramuscular injections with 5 × 10e10 viral particles or 1 × 10e11 viral particles of Ad26.COV2.S. By day eight following immunisation, binding antibodies against full-length S protein were observed in 65% of vaccine recipients and against the S receptor-binding domain (RBD) in 90% of vaccine recipients.Virus-neutralising antibodies were observed in 25% of vaccine recipients. By day 15, S-specific and RBD-specific binding antibodies were observed in 100% of vaccine recipients, and neutralising antibodies were observed in 85% of vaccine recipients. Binding and neutralising antibodies continued to increase on days 29, 57, and 71. By days 57 and 71, 100% of vaccine recipients showed neutralising antibodies and S- and RBD-specific binding antibodies. The boost dose on day 57 increased binding antibody titres by 2.56-fold and neutralising antibody titres by 4.62-fold. Detailed assessment of antibodies type showed that Ad26.COV2.S induced S- and RBD-specific IgA1, IgA2, IgG1, IgG2, IgG3, IgG4, and IgM subclasses; FcγR2a, FcγR2b, FcγR3a, and FcγR3b binding. Antibody-dependent complement deposition, neutrophil/monocyte phagocytosis, NK cell activation and functional antiviral responses were observed together with the induction of central memory CD27+/CD45RA−/CD4+ and CD8+ T-cell responses. IFN-γ responses were observed in 65% of vaccine recipients by day 15 and in 84% of vaccine recipients by day 71 [82].

ChAdOx1 Nov-19 (Astra-Zeneca): Anti-spike IgG antibodies to SARS-CoV-2 spike and receptor-binding domain (RBD) titres rose after the first vaccination, with a further increase after the second. Vaccination increased anti-spike IgM and IgA titres with a peak response 28 days after priming. IgG1 and IgG3 responses were detectable on day 28 and remained at a similar level before boosting. Neutralising antibodies were induced following prime vaccinations and significantly increased after the booster dose. Anti-spike antibody function was explored to determine the ability of antibodies induced by vaccination to support antibody-dependent monocyte and neutrophil phagocytosis. Both functions were induced by the first vaccination and substantially increased by the second dose. Antibody-dependent complement deposition was also induced by prime vaccination and increased following booster doses. Single-dose ChAdOx1 nCoV-19 induced low anti-spike antibody-dependent NK cell activation, boosted by the second dose given either on day 28 or day 56. Antigen-specific T cell responses measured by IFN-γ were induced and peaked 14 days after the first dose [83],[46].

Gam-COVID-Vac (Sputnik V): RBD-specific IgG were detected in 98% samples and neutralising antibodies in 95%. Cellular immune response was evaluated with the secretion of IFN-γ of peripheral blood mononuclear cells upon stimulation with SARS-CoV-2 glycoprotein S. By day 28 after the first vaccination, all participants had significantly higher levels of IFN-γ secretion compared with the day of administration of the first dose [45].

CoronaVac: Antibody titres of neutralising antibodies to live SARS-CoV-2 and RBD-specific IgG were induced after two doses on days 0 and 14 and days 0 and 28 in adults 18-59 years old. Data showed persistence of neutralising antibody titres beyond 28 days. Seroconversion of neutralising antibodies was seen for 92% of participants receiving the 3 μg dose of vaccine, and in 98% receiving the 6 μg dose. Neutralising antibody titres induced by the 3 μg dose were similar to those of the 6 μg dose, supporting the use of the 3 μg dose CoronaVac in phase 3 trials to assess protection against COVID-19. At 14 days after the second dose of study, the levels of IFN-γ were measured. T-cell responses were low in participants given the vaccine, which provided no clear evidence that the vaccine induced T-cell answers [84]. Similar observations were made in the group of adults over 60 years of age [46].

In summary, the levels of antibodies (binding Ab specific to S-2P protein and neutralising Ab) were assessed on different days after the first dose of the vaccine (from day 7 to 40) and at various time points after the booster dose, up to 3 months. The antibody levels rise at least until day 28. Limited data available after day 28 show antibody increase up to day 40 after the first dose (Moderna, Pfizer).

B. Potential effects of COVID-19 vaccination on AIT

Safety and efficacy are crucial for an allergic patient under AIT, who (plans?) to receive an anti-infectious vaccine (AIV).

Current guidelines recommend that administration of AIT and AIV should be separated by a minimum of a 7-day interval [85]. This recommendation is based on the hypothesis that AIV may act as a co-factor of an allergic reaction to AIT, as it can happen with "natural" infection and other stimuli (e.g., exercise), a mechanisms well-established for food-dependent exercise-induced anaphylaxis or for oral food immunotherapy induced anaphylaxis [86]. However, this is based on a pragmatic approach rather than on existing evidence from clinical studies. A retrospective analysis of 875 subjects showed that patients receiving AIT and AIV on the same day did not experience more systemic reactions than those receiving AIT alone [87]. Data on AIV impact on AIT suggest that booster vaccines can be effectively and safely administered in allergic patients receiving AIT [88]. From the mechanistic point of view, AIT and COVID-19 immune responses do not seem to interfere negatively. AIT patients might even benefit by rebalancing the innate immune system and favouring protective responses (Table 1, figures 2 and 3).

No data on the effects of AIT on the COVID-19 vaccine-induced antibody production are available. Due to different antigen specificity, it can be speculated that there is no interference. The data on the inflammatory marker induction, e.g. CRP protein, IL-1, TNF-α, are very limited. Consequently, it is not possible to recommend the interval between AIT and COVID19-vaccination based on objective measures. This should be considered on a case by case basis. Studies show that the COVID-19 vaccines elevate IFN-γ production but have no influence on IL-4 production. This might account for the synergistic effect of COVID-19 and AIT.

<u>Recommendation 1:</u> COVID-19 vaccines should be administered at the interval of 7 days from the subcutaneous allergy vaccines to unequivocally assign potential side effect of each one. Likewise, sublingual daily dose should be stopped 3 days before COVID-19 vaccine administration and restarted 7 days after.

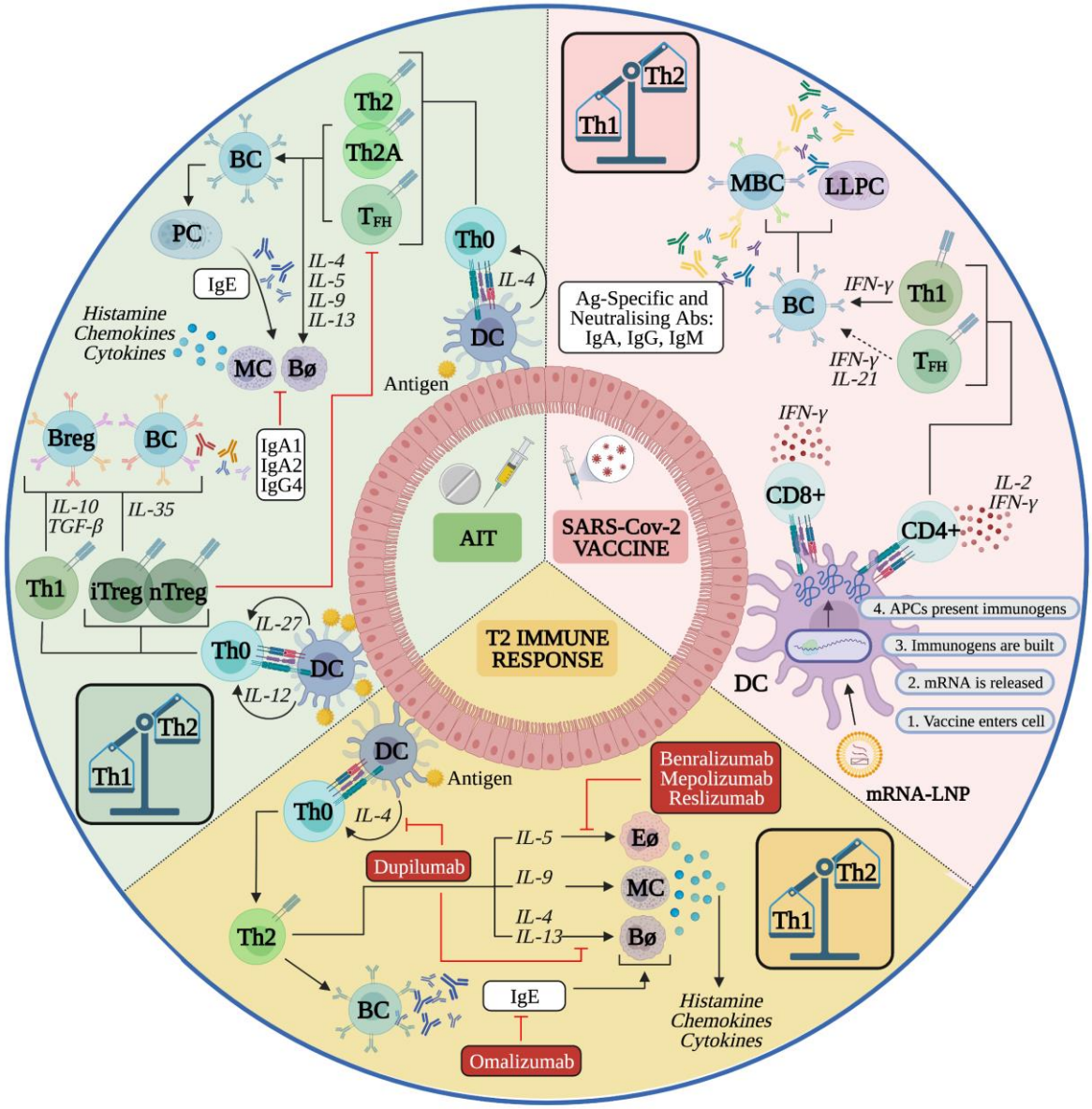

Figure 2. Immune modulatory responses of COVID-19 vaccination, allergen immunotherapy and Biologicals T2 responses.

Reslizumab, mepolizumab and benralizumab are anti-IL-5/IL-5 receptor targeted biologicals. Dupilumab is an IL-4 α subunit receptor targeted biological treatment which inhibits the action of the IL-4 and IL-13. Omalizumab is an anti-IgE biological treatment. Red inhibition lines indicate where these five biologicals elicit inhibitory actions within the T2 allergic response. Biological inhibition of the T2 immune response deviates to a Th1-driven cellular response.

AIT, administered subcutaneously or sublingually, results in an increased allergen-load captured by DC, skewing naïve Th0 cell differentiation into iTreg, nTreg cells and Th1 cells in the setting of IL-27 and IL-12. iTreg, nTreg cells and Th1 cells release anti-inflammatory cytokines IL-10, IL-35 and TGF-β, which induce class-switching in Breg and BC cells to IgA1, IgA2 and IgG4. IgA1, IgA2 and IgG4 inhibit IgE-cross linking, preventing effector cell activation. iTreg and nTreg cells also inhibit T_{FH} and Th2 cellular responses. AIT therefore causes immunodeviation to a Th1 cellular response due to increased allergen exposure.

During SARS-Cov2 vaccination, mRNA-LNP (encoding SARS-Cov2 modified spike (S) protein) enters the cell and releases its mRNA. The host-APC then builds the encoded immunogens, and presents them on MHC I to CD8+ T-cells which subsequently secrete antiviral IFN-γ. DC also present the encoded immunogen antigen on MHC II to CD4+ T-cells, which secrete IFN-γ and IL-2, and differentiate into T_{FH} and Th1 cells. T_{FH} and Th1 cells release IFN-γ and IL-21, promoting B-cell isotype class-switching to SARS-Cov-2 S protein specific and neutralising antibodies; IgA, IgG and IgM. B-cells with high affinity are positively selected and further differentiate into LLPC and MBC. The SARS-Cov2 vaccination immune pathway is therefore mediated through a Th1 cellular response.

T2; Type 2; DC, Dendritic Cell; Th0, naïve T Cell; BC, B Cell; Breg, regulatory B cell; MC, Mast Cell; MHC, Major Histocompatibility Complex; Eθ, eosinophils; Bθ, basophil; Th2, T helper Type 2 cell; Th1, T helper Type 1 cell; Ig, immunoglobulin; T_{FH}, T Follicular helper cell; iTreg; induced regulatory T cell; nTreg, natural regulatory T cell; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TGF-β, transforming growth factor β; TNF-α; IFNγ, Interferon-γ; IL, Interleukin, T_{FR}, T Follicular regulatory cell, long-lived high affinity plasma cells (LLPC); MBC, Memory B-cell; mRNA-LNP, lipid nanoparticle.

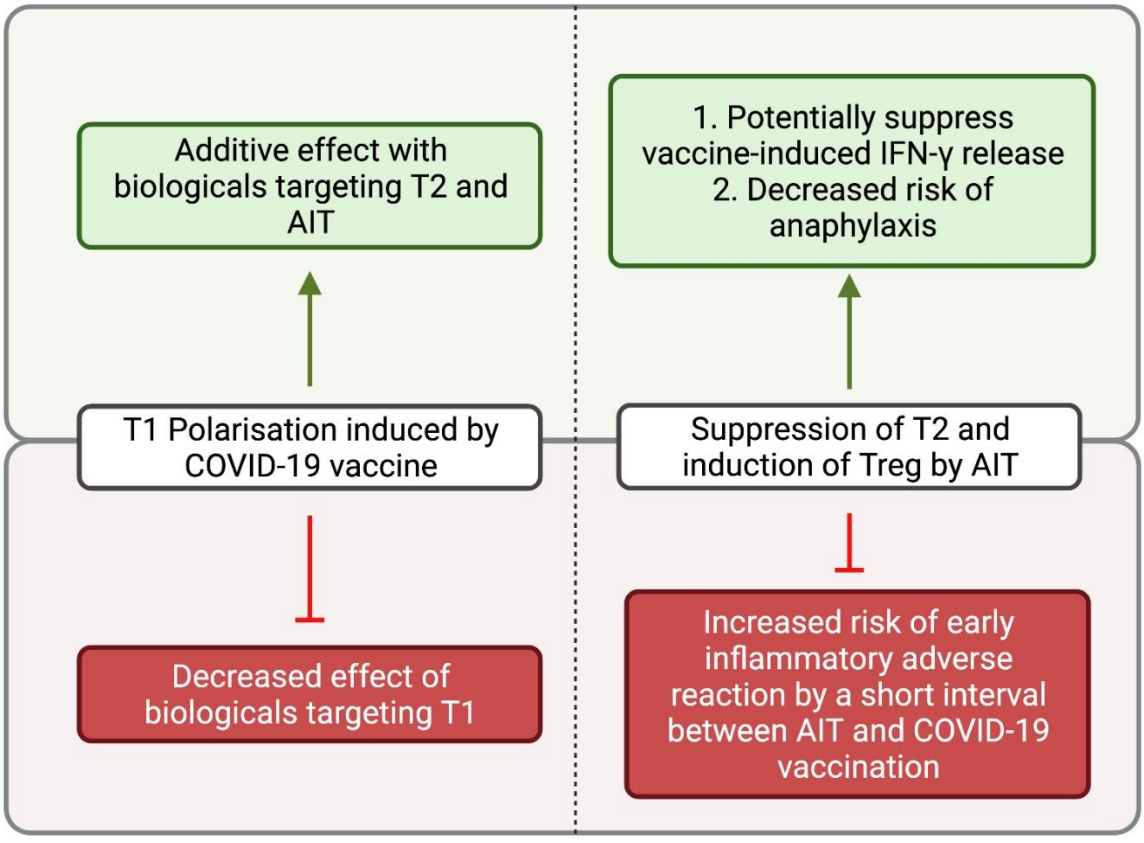

Figure 3: The potential impact of the COVID-19 vaccination on the efficacy and safety of AIT and biological treatment.

SARS-CoV-2 vaccine has been demonstrated to induce T1 polarisation. Therefore, through increasing T1 immunity, the COVID-19 vaccine may decrease the effect of biologicals targeted against T1 inflammation. Moreover, T1 polarisation may provide an additive effect to AIT and biologicals which target T2 immunity. It can be postulated that the suppression of T2 immunity and induction of Treg cells observed during AIT may increase the risk of early inflammatory adverse reactions by a short interval.

Moreover, the reduction of T2 immunity may potentially suppress vaccine-induced IFN-γ release and decrease the risk of anaphylaxis. T1, Type 1; T2, Type 2; Treg, T regulatory cells; AIT, Allergen immunotherapy; IFN-γ, Interferon-γ.

C. Potential effect of COVID-19 vaccine on biological therapies targeting the T2 immune response

Five mAbs are currently approved for severe Type 2 asthma: omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab [89]. The use of these mAbs during the COVID-19 pandemic is considered safe, as they do not increase the rate of viral transmission [90], [91]. Conversely, international guidelines recommend the withdrawal of these drugs in case of active SARS-CoV-2 infection because of reports of delayed and diminished anti-SARS-CoV-2 antibody production in asthmatic patients who became infected while receiving mAbs [92], [93]. In a series of 4 cases, asthmatic patients on mepolizumab experienced COVID-19 of varying severity [94]. However, the production of anti-SARS-CoV-2 antibodies was not investigated. The inhibition of Type 2 response in severe and critical COVID-19 cases may cause an aggravation of the disease and hamper recovery. Therefore, EAACI recommends that such biologicals should be discontinued until the COVID-19 infection is cleared. Due to their long in vivo half-life in the range of a few weeks, it remains unclear to which extent such an action would impact acute management and what the risk of losing disease control and comorbidity, later on, could be.

Interestingly the upregulation of IgE, IL-5, IL-13 and eosinophils have been reported in severe COVID-19 [66]. Although eosinopenia is not an exclusive feature of severe COVID-19, a reduced number of eosinophils has been associated with worse outcomes of COVID-19, while their restoration precedes recovery [95], [96]. Moreover, eosinophils may play a role in virus recognition, presentation and clearance [97]. Thus, IL-5 targeting biologicals mepolizumab and reslizumab and the IL-5 receptor targeting mAb benralizumab could affect the antiviral response. This hypothesis has not been supported by *in vivo* data [98], [99], [100], [101]. However, the increased pulmonary presence of eosinophils and acute eosinophilic pneumonia in post-mortem findings after SARS-CoV-2 indicate that IL-5-induced reduction in eosinophils might be beneficial in the pathological response in the lung. Vaccines for the previous SARS-COV have been associated with an immunopathology eosinophilic lung infiltrate. This point should be considered in the development of a vaccine strategy for COVID-19 [102].

Very few data are available regarding AIV administration while receiving anti-T2 mAbs. Evidence for the safety of the biologicals and vaccine responses is available for omalizumab, dupilumab and benralizumab, with no proof yet of a negative impact of the respective biological on the vaccine response [103], [104].

Omalizumab has been linked to positively affect pDC-dependent interferon Type I production in asthmatics and CSU patients [105]. It may even restore reduced Type I interferon production in patients with allergic diseases, thereby supporting antiviral immune responses. Omalizumab has been used in several AIT trials as co-medication to reduce IgE-mediated side effects. Current data from AIT trials do not suggest that omalizumab impacts allergen-specific IgG responses and T-cell responses outside of the AIT related immunomodulation. In addition, on a case report basis, omalizumab was applied successfully to treat COVID-19 driven urticaria [106].

A preclinical study showed that omalizumab does not affect the ability of T and B cells to mount protective responses after vaccination with tetanus toxoid (Novartis, data on file). Moreover, published trials of omalizumab did not consider the recent AIV administration course as an exclusion criterium. Therefore, several AIV (diphtheria, inactivated hepatitis B, tetanus toxoid, influenza, or pneumococcal vaccines) were administered within the trial period, without specific reports of adverse events [107]. Nevertheless, this is not sufficient to guarantee that omalizumab does not impair the production of protective antibodies after AIV. There are only limited data available on vaccination safety under Omalizumab: A recent small retrospective study reported the safety of yellow fever vaccination under omalizumab treatment for CSU [108]. Omalizumab inhibits FcεRI expression on DCs and, very

significantly, restores the capacity of plasmacytoid DCs (pDCs) to produce high levels of Type I IFN-α [109], [110], which has been associated with the reduction of asthma exacerbations triggered by viral infections [111], [112]. Omalizumab also restores *in vitro* the capacity of atopic pDCs to polarize Treg cells, contributing to proper antiviral immune responses [113].

In a double-blind, placebo-controlled study in 87 and 91 patients with atopic dermatitis treated with dupilumab and placebo respectively, received subcutaneous Tdap (tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine) or meningococcal polysaccharide vaccine after 12 weeks of treatment. At week 16, the proportion of patients showing satisfactory IgG responses against both infectious agents and the median titles of the protective antibodies were similar in both groups [114] (table 2).

<u>Recommendation 2:</u> A 7 day interval between administration of a biological targeting the T2 immune response and COVID-19 vaccine is recommended to unequivocally assign potential side effects of each other.

<u>D. Potential effect of COVID-19 vaccination on biologicals targeting non-Type 2 inflammation</u>

Applying biologicals in non-type 2 inflammatory diseases may interfere significantly both with the antiviral and the vaccine responses. Therapeutics affecting cell trafficking (e.g. natalizumab) may reduce local viral clearance. Anti-cytokine antibodies (anti-TNF-alpha, anti- IL1beta, anti-IL6) can suppress antiviral cellular responses and secondary humoral responses. On the other hand, autoimmune inflammatory conditions may negatively impact vaccine responses and treatment may theoretically restore and promote a more robust vaccine response. Although patients with immune-mediated inflammatory conditions seem to develop less commonly COVID-19, severity and mortality are increased compared to the general population once they acquire it, especially if the disease is not controlled with background therapy [115].

Depletion of B-cells via the anti-CD20 biologicals such as rituximab, obinutuzumab, ocrelizumab and ofatumumab or biosimilars are anticipated to impact COVID-19 vaccine responses as they efficiently suppress early IgM, IgG and IgA responses. In B-cell depletion, vaccine response is dependent on the number of B-cells still “available”; thus “, titration” of the induced immune suppression is of note. Patients on these treatments have per se a higher risk to develop severe or fatal COVID-19 due to concomitant risk factors and or additional systemic immune suppression. An increased risk of hospital and ICU admission following COVID-19 infection has been reported for rituximab and ocrelizumab (OR 2.37) and recent usage of methylprednisolone (<1 month; OR 5.24), but not for other disease-modifying drugs used for multiple sclerosis [116].

A recent systematic review on the impact of COVID-19 on demyelinating diseases highlighted the complexity of estimating risks associated with immunomodulatory treatment in these patient groups regarding the severity of COVID19 infection. It reported higher mortality in rituximab treated patients (4%) vs the overall multiple sclerosis (MS) population (1.8%) [117]. Data from the post-marketing safety, real-world data and clinical trials on ocrelizumab reported comparable mortality rates compared to the normal population, and the non-ocrelizumab treated MS population [118]. The VELOCE study investigated the impact of ocrelizumab on responses to a 23-valent pneumococcal polysaccharide vaccine (23-PPV; not received within >5 years) or the 13-valent conjugate pneumococcal vaccine (13-PCV), tetanus toxoid (TT) containing vaccines (not applied for >2 y) and influenza vaccine (no vaccination last two seasons) by comparing it in MS patients on INFbeta/ no additional therapy. Ocrelizumab significantly reduced vaccine responses, but an appropriate number of patients could mount an antibody response to TT (24% vs 55%), a neoantigen, an influenza vaccine (56 vs 80%). In the pneumococcal vaccines, there

was a reduced response to serotypes from 23-PPV (75% vs 100% pos response to >5 serotypes) reported but not for the 13-PCV [119].

In the context of inflammatory diseases, TNF-alpha suppresses B- and T-cell function, which can be restored by anti-TNF-alpha treatment [120], [121], [122]. Undesired effects of this treatment on vaccine responses are not anticipated. Nevertheless, reduced pathogen-related responses and an increased risk for specific pathogens to cause severe disease has been reported under anti-TNF-alpha treatment due to its pleiotropic effect on immune responses to pathogens (e.g. *Mycobacterium tuberculosis*). Patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) receiving anti-TNF-alpha antibodies experience reduced response/seroconversion rates to influenza vaccines; hepatitis B vaccine compares to other treatment regimens in this cohort. However, a significant percentage of patients on this treatment can mount protective vaccine titres [123], [124], [125]. Data on certolizumab suggests that pneumococcal and influenza vaccine responses were not impaired when applied during therapy initiation [126]. A systematic review on biologicals on vaccine responses in the context of autoimmune inflammatory rheumatic diseases concluded that vaccine responses to influenza and pneumococcal vaccine are adequate under anti-TNF-alpha drugs, tocilizumab (anti-IL6) and belimumab (anti-BAFF; data only for the pneumococcal vaccine) [127]. Accurate vaccine treatment responses have also been reported under treatment with ustekinumab in Crohn's disease patients [128] and secukinumab in patients with psoriatic arthritis [129] or ankylosing spondylitis [130].

Immune checkpoint inhibition (ICI) via anti-PD-1/anti-PD-L1 and or CTLA reduces immune-regulatory responses to benefit better anti-neoplastic responses. Thus, viral responses could even be enhanced. COVID-19 morbidity and mortality are considered comparable in oncological patients on ICI than matched patient groups who are not on this treatment [131]. Vaccine response data are scarce. A recent systematic review reported a normal humoral response and an increased seroconversion under ICI. The majority of investigations focused on influenza vaccines. Notably, the rate of immune-related adverse events was elevated [132]. CLTA-4 targeting therapy via abatacept in AIRD was associated with a mildly reduced vaccine response in a systematic review based on controversial data with low evidence.

In summary, non-Type 2 diseases encompass a paramount of immune dysregulation and treatment approaches with biologicals. Most of the biological-based therapies either affect vaccine responses only mildly or not significantly. Robust evidence for a reduced considerably yet not abolished vaccine response is reported for B-cell depleting therapies.

<u>Recommendation 3:</u> A 7 day interval between administration of biological targeting the non-Type 2 immune response and COVID-19 vaccination is recommended to unequivocally assign potential side effect of each other.

<u>Conclusions:</u>

EAACI recommendations are based on the mechanistic evaluation as well as clinical experience and evidence involving other anti-infective vaccines.

The current assessment does not suggest any relevant interference compromising neither the safety nor the efficacy of AIT, biologicals or COVID-19 vaccines.

Further evidence from disease registries and other real world data bases must be accumulated in order to refine current recommendations.

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838 Table 1. COVID-19 vaccines and immunological effects [133].

Vaccine platform	Name/Manufacturer	Administration route	Immunological mechanism	Ref
Approved or in Phase 3 clinical trials				
mRNA	1. BNT162; Pfizer/BioNTech 2. mRNA -1273; Moderna + NIAID 3. CVnCoV; CureVac AG	im	Antigen-specific cytotoxic $CD8^+$ T cells (IFN-γ released) Antigen-specific $CD4^+$ T cells (Th1; Th2-not detected) Antigen-specific and neutralizing antibodies	31 32 34 42
Recombinant viral vectors (Viral vector non-replicating)	1. ChAdOx1 nCoV-19 (AZD1222) (Astra Zeneca + University of Oxford) 2. Recombinant novel coronavirus vaccine (Adenovirus type 5 vector); CanSino Biological Inc./Beijing Institute of Biotechnology 3. Gam-COVID-Vac (Sputnik V) Adeno-based (rAd26-S+rAd5-S); Gamaleya Research Institute; Health Ministry of the Russian Federation 4. Ad26.COV2.S; Janssen Pharmaceutical (Janssen/Johnson &Johnson)	im	Antigen-specific cytotoxic $CD8^+$ T cells (IFN-γ released) Antigen-specific $CD4^+$ T cells (Th1; Th2-not detected) Antigen-specific and neutralizing antibodies	45 46 82
Inactivated vaccine virus	1. SARS-CoV-2 vaccine (inactivated); Sinovac Research and Development Co., Ltd 2. Inactivated SARS-CoV-2 vaccine (Vero cell); Sinopharm+ China National Biotec Group Co + Wuhan Institute of Biological Products 3. Inactivated SARS-CoV-2 vaccine (Vero cell), Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products 4. SARS-CoV-2 vaccine (vero cells); Institute of Medical Biology + Chinese Academy of Medical Sciences	im	?	

	5. QazCovid-in® - COVID-19 inactivated vaccine; Research Institute for Biological Safety Problems, Rep of Kazakhstan 6. Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152); Bharat Biotech International Limited			
Subunit (recombinant protein vaccines)	1. SARS-CoV-2 rS/Matrix M1-Adjuvant (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M) (Novovax) 2. Recombinant SARS-CoV-2 vaccine (CHO Cell); Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences 3. SCB-2019 + AS03 or CpG 1018 adjuvant plus Alum adjuvant (Native like Trimeric subunit Spike Protein vaccine) ; Clover Biopharmaceuticals Inc./GSK/Dynavax 4. UB-612 (Multitope peptide based S1-RBD-protein based vaccine); COVAXX + United Biomedical Inc	im	?	
Less advanced COVID-19 vaccine candidates				
Viral-like Proteins (VLP)	1. Coronavirus-Like Particle COVID-19 (CoVLP); Medicago	im	?	
Live-attenuated	1. Codagenix/Serum Institute of India-phase I_NCT04619628	im	?	
Recombinant viral vectors (Viral vector (Replicating)	1. Coronavirus-Like Particle COVID-19 (CoVLP); Medicago Inc. 2. RBD SARS-CoV-2 HBsAg VLP vaccine; Serum Institute of India + Accelagen Pty + SpyBiotech	im	?	

Table 2. Summary of studies on patients under treatment with AIT / biologicals receiving anti-infectiousvaccines.

Treatment	Vaccine	Underlying disease	Patients number	Conclusion
Allergen Immunoterapy *(Garner-Spitzer, 2018)* [88]	Booster of tick-borne encephalitis	Allergic rhinoconjunctivitis and asthma	119 (49 allergic, 21 allergic on AIT and 49 non-allergic)	No effect of AIT on antibody response

Omalizumab *(Criado PR, 2019)* [106]	Yellow fever	CSU	28	No cases of mild yellow fever
Omalizumab *(Turner P, 2020)* [107]	Live attenuated influenza	Moderate-severe asthma	478	Well tolerated
Dupilumab (*Blauvelt A, 2019*) [114]	-Tdap (tetanus toxoid, reduced diphteriua toxoid, acellular pertussis vaccine) - meningococcal polysaccharide vaccine	Atopic dermatitis	87 treated by dupilumab / 91 with placebo	Satisfactory and equal IgG response with or without dupilumab 4 weeks after injection

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843 Table 3. Immunological characteristics of AIT and COVID-19. (put to the supplement)

	AIT	**Biologicals targeting T2 inflammation**	**COVID-19**	**COVID-19 vaccine**
Immunological changes	▪ No impact on the whole immune system; no systemic immune deficiency ▪ response targets allergen-specific T and B	▪ No impact on the whole immune system (only on specific blocked pathways); no systemic immune deficiency reported ▪ Response targets specific T2 pathways: IgE (Omalizumab), IL-4Rα (Dupilumab), IL-5 (Mepolizumab, Reslizumab), IL-5Rα (Benralizumab), Alarmins (anti-TSLP or anti-IL33 under development)	▪ does not significantly increase the severity of allergic disease ▪ the disruption of Type 1 and innate antiviral immunity plays a role in the pathogenesis and severity of COVID-19	▪ The formation of high-affinity long-lived plasma cells (LLPCs) and memory B cells (MBCs) ▪ Induced a dose-dependent SARS-CoV-2-specific Ab response ▪ Germinal Center-derived B cell response induced by SARSCoV-2 mRNA vaccines
T cell responses	▪ decreases allergen-specific Type2 responses (Th2 cells and ILC2) in circulation and	▪ Decreases expansion and activation of memory Th2 responses (Omalizumab	▪ CD4 and CD8 T cells decrease (lymphopenia in severe cases) ▪ inhibition of IFN-γ signaling	▪ T follicular helper (Tfh) cells are crucial regulators of GC and affinity-

	in the affected organs such mucosal tissues ▪ induction of allergen-specific Treg ▪ together with B regulatory cells T regs create a tolerogenic milieu: by the release of IL-10, TGF-β and by direct cell contact mediated bymolecules like CTLA-4 and PD1 ▪ switch between Type2 and Type 1	and Dupilumab) and effector responses by directly or indirectly blocking specific effector cytokines (all of them). ▪ Induction of Treg cells (showed in vitro for Omalizumab)	results in reduced antiviral response and ongoing pro-inflammatory response ▪ excessive inflammation and worsening of the disease ▪ decreased number of Treg cells ▪ progressive increase in follicular helper T (TFH) in non-severe COVID-19 ▪ in severe disease a systemic severe inflammatory response occurs with a cytokine release syndrome (CRS) - Type 1 and Type 3-driven ▪ these inflammatory responses are potentially counteracted by anti-inflammatory cytokines, such as IL-10 and TGF-β, and potentially by Type 2 responses which facilitate recovery	matured Ab responses ▪ Other CD4 T cell subsets might serve different important functions, including facilitating optimal CD8 T cell responses ▪ SARS-CoV-2 mRNA-LNP vaccines favor the functional polarization of total CD4 T cells toward Th1, while Tfh cells are characterized by the production of both Th1 (IFNgamma) and Th2 (IL-4) cytokines
CD8+ T cells	▪ No major change	▪ Inhibition of tissue and mucosal infiltration of CD8 + T cells and Tc2 in particular.	▪ total number of NK and CD8+ T cells markedly decreased in severe COVID (functional exhaustion of cytotoxic T lymphocytes)	▪ No indication that the induction of cytotoxic CD8 T cells is required for successful protection against SARS-CoV-2 via vaccination

Th1 – Th2 response	▪	▪ Specific blocking of Th2 responses.	▪	▪ Th1- and Th2-biased Tfh cells are both relevant in shaping a neutralizing response to SARS-CoV-2 ▪ mRNA-LNP vaccines skewed Tfh cells towards a Th1 phenotype when using full-length S D furin as immunogen, or towards a mixed Th1/Th2 phenotype when RBD was the immunogen ▪ rRBD-AddaVax induced Th2-biased Tfh cells

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