Journal of Medical Toxicology (2023) 19:205–218
https://doi.org/10.1007/s13181-023-00931-9

REVIEW

COVID-19 Therapeutics: Use, Mechanism of Action, and Toxicity (Vaccines, Monoclonal Antibodies, and Immunotherapeutics)

Michael Chary[1,2,3,4] · Alexander F. Barbuto[1,2,5] · Sudeh Izadmehr[6] · Marc Tarsillo[3] · Eduardo Fleischer[1] · Michele M. Burns[1,2,7]

Received: 23 August 2022 / Revised: 2 February 2023 / Accepted: 6 February 2023 / Published online: 2 March 2023

Abstract

SARS-CoV-2 emerged in December 2019 and led to the COVID-19 pandemic. Efforts to develop therapeutics have led to innovations such as mRNA vaccines and oral antivirals. Here we provide a narrative review of the biologic therapeutics used or proposed to treat COVID-19 during the last 3 years. This paper, along with its companion that covers xenobiotics and alternative remedies, is an update to our 2020 paper. Monoclonal antibodies prevent progression to severe disease, are not equally effective across variants, and are associated with minimal and self-limited reactions. Convalescent plasma has side effects like monoclonal antibodies, but with more infusion reactions and less efficacy. Vaccines prevent progression for a larger part of the population. DNA and mRNA vaccines are more effective than protein or inactivated virus vaccines. After mRNA vaccines, young men are more likely to have myocarditis in the subsequent 7 days. After DNA vaccines, those aged 30–50 are very slightly more likely to have thrombotic disease. To all vaccines we discuss, women are slightly more likely to have an anaphylactic reaction than men, but the absolute risk is small.

Keywords Covid-19 · Vaccines · Immunotherapy · Monoclonal antibodies

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus that causes coronavirus disease 2019 (COVID-19), a respiratory infection that can progress to acute respiratory distress syndrome (ARDS), myocarditis [1, 2], or death.

One year into the pandemic the United States Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Pfizer's vaccine, marking a shift in efforts from repurposing medications to widespread vaccination. One month later, the FDA issued EUAs for Moderna's vaccine and for monoclonal antibodies designed to prevent disease progression in those infected with SARS-CoV-2 with mild symptoms and major comorbidities. The speed of development and effectiveness of vaccines has been matched by public resistance to receiving the vaccine and misinformation [3], mostly over-emphasizing the adverse effects of the vaccine and downplaying the risks of untreated COVID-19, a calculus that also changes with each variant [4].

This narrative review describes the effects of vaccines and monoclonal antibodies that a clinician is likely to encounter

Supervising Editor: Michael Hodgman, MD

✉ Michael Chary
mic9189@med.cornell.edu

1 Division of Medical Toxicology, Department of Emergency Medicine, Boston Children's Hospital, Boston, MA, USA

2 Regional Center for Poison Control and Prevention Serving Massachusetts and Rhode Island, Boston, MA, USA

3 Department of Emergency Medicine, Weill Cornell Medical College, New York, NY, USA

4 Department of Emergency Medicine, New York Presbyterian Queens, Flushing, NY, New York, USA

5 Department of Emergency Medicine, Carl R. Darnall Army Medical Center, Fort Hood, TX, USA

6 Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

7 Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA, USA

when treating patients affected by COVID-19. We focus on toxicity, not efficacy.

Methodology

In our previous publication we discussed the recombinant protein APN01, humanized antibody leronlimab, nucleotide analogs remdesivir and favipiravir, protease inhibitors lopinavir/ritonavir, DNA vaccines (S-trimer, INO-4800, GLS-5300), the Moderna mRNA vaccine, and convalescent plasma [5]. In the last 2 years, the monoclonal antibodies, protein vaccines, and more mRNA vaccines emerged. For each of these substances, we searched PubMed and Google Scholar for any publications between May 1, 2020, and June 1, 2022 that mentioned the substance and contained the keywords "adverse event," "secondary effect," "unintended effect," "adverse reaction," "unintended reaction," or "toxicity," or their spelling variants, in the full-text of the paper. We considered papers tagged with MeSH Heading "Drug Toxicity" (D064420), also labeled as "Adverse Drug Event," and all subheadings. This MeSH heading also includes all adverse drug reactions, which are the intersection of the MeSH tags D064420 and D004347 ("Drug Interaction"). We only considered peer-reviewed publications for which the full-text in English was available. We also included each vaccine's application for Emergency Use Authorization by the FDA.

We included substances we did not previously discuss, choosing based on the vaccines being recommended by the Center for Disease Control and our experience as practicing physicians and scientists. Our description of substances and their effects is not exhaustive and presents our knowledge as of June 2022. In the absence of direct evidence, we expect drugs of a similar class to have similar toxicity. Our search strategy may be biased towards mild and moderate effects, which are assiduously reported by clinical trials. We include case reports even though they cannot demonstrate causality, because they often provide the first description of severe toxicity.

Biology of Coronavirus Spike (S) Protein

SARS-CoV-2 is an enveloped non-segmented positive-sense RNA virus that belongs to the Coronavirinae family. Its genetic sequence resembles SARS-CoV-1, a beta-coronavirus that caused the SARS (Severe Acute Respiratory Syndrome) epidemic in 2003. To date, vaccines have focused on raising immunity against the S protein, the protein SARS-CoV-2 uses to attach to and enter host cells. The S protein is an attractive target because it elicits an immune response and mutations in it may explain the variation in virulence across SARS-CoV-2 strains. It is a trimeric glycosylated transmembrane complex embedded in the lipid bilayer that surrounds the viral genome. Understanding the structure is important for understanding the toxicity of monoclonal antibodies that bind to specific parts of the S protein, which creates the potential for each monoclonal antibody to have unique off-target effects. The S protein is composed of a region that attaches to the ACE2 receptor (the receptor binding domain (RBD) or S1) and a region that facilitates fusion of the host and virus membranes (S2) [6]. The parts of the S protein mutate at different rates, explaining why the efficacies of monoclonal antibodies and vaccines, which assume a specific S protein sequence, differ across SARS-CoV-2 variants. The S protein is glycosylated, which helps it evade detection by the immune system and tightly bind to ACE2 receptors [7]. It is challenging to develop antibodies against glycosylated proteins because the sugars coat the immunogenic protein and vary too frequently in structure to be themselves a viable target.

COVID-19 Therapeutics

APN01

APN01 is a recombinant human ACE2 protein first developed to treat SARS-CoV-1. It was hoped that APN01 would prevent SARS-CoV-2 from entering the cell just as it did for the structurally similar SARS-CoV-1. The proposed mechanism was that APN01 would act as a decoy for the virus, much as andexanet alfa acts as a decoy for factor Xa inhibitors. A randomized unblinded clinical trial was reported underway in 2020 in the People's Republic of China [8]. We could find no toxicity data to present. Absent new data, we reiterate the general observation that toxicity from recombinant proteins results from inadvertently activating the immune system and off-target binding, which may manifest as type II or III hypersensitivity.

Convalescent Plasma

Convalescent plasma is plasma pooled from those who contracted and then recovered from COVID-19. It is administered to patients who have contracted the disease and are at high risk for deterioration without intervention. The rationale behind convalescent plasma is like that for monoclonal antibodies, as convalescent plasma is a mélange of immunoglobulins. Case series report that self-limited chills and fevers are the main adverse events [9].

The general risks associated with plasma transfusion are acute lung injury, circulatory overload, allergic/anaphylactic reactions, transmission of infections, febrile hemolytic and non-hemolytic transfusion reactions, and

RBC alloimmunization. An analysis of 50,000 hospitalized patients with COVID who received convalescent plasma through the FDA's Early Access Program reported transfusion reactions ($n=78$), thromboembolic or thrombotic events ($n=113$, 75 judged unrelated), and cardiac events ($n=677$; 597 judged unrelated), mainly myocarditis and acute coronary syndrome [10].

Monoclonal Antibodies

Monoclonal antibodies supplement the body's immune response by helping the body identify SARS-CoV-2 virus particles, in effect providing ready-made beacons to the immune system while it is developing its own [11]. In December 2021, the FDA issued an EUA for sotrovimab [12], bamlanivimab/etesevimab [13], and casirivimab/imdevimab [14] to treat non-hospitalized immunosuppressed patients who are at high risk for progression of COVID-19 symptoms. Bamlanivimab/etesevimab and casirivimab/imdevimab bind to the receptor binding domain [15]. Sotrovimab binds to the S2 subunit [16].

Antibody toxicity can arise from an expected effect on the target, an immunologic response to the antibody, or from off-target binding. An example of of an expected but undesired effect is immunosuppression from infliximab, which targets TNF-alpha, leading to more frequent infections. Examples of an immunologic response to the antibody itself include hypersensitivity reactions, complement activation, and cytokine storm. Cytokine storm refers to fevers, chills, myalgias, and acute lung injury resulting from direct activation of various immunocompetent cells including macrophages, monocytes, lymphocytes, and natural killers (NK) cells. Cetuximab, an anti-EGFR monoclonal antibody used to treat head and neck cancer illustrates adverse effects from off-target binding. Cetuximab also binds to EGFR receptors in the skin leading to reactions as varied as pruritus, hirsutism, and xerosis. As another example, trastuzumab, an anti-her2 monoclonal antibody used in the treatment of breast cancer, binds to cardiac her2 receptors leading to dysrhythmias and cardiomyopathy [17].

Leronlimab (PRO 140)

Leronlimab is a humanized IgG4 monoclonal antibody that decreases IL-6 production by targeting the T cell CCR5 receptor [18]. To date, no clinical trials have been performed. Of 23 patients who received one subcutaneous injection of 700 mg leronlimab on a compassionate use basis, 17 recovered at day 30 although IL-6 levels did not decrease after administration. Eighteen of the 23 were also receiving convalescent plasma, remdesivir, tocilizumab, hydroxychloroquine, or sarilumab [19]. Four patients with SARS-CoV-2 on mechanical ventilation and vasopressors were able to be extubated and weaned off pressors after receiving two infusions of 700 mg leronlimab two weeks apart and IL-6 levels decreased, but these patients also received hydroxychloroquine, zinc, tocilizumab, remdesivir, and azithromycin [20]. Neither publication presented data on adverse events.

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody that binds to the IL-6 receptor [21]. Macrophages secrete IL-6 when they detect an entity whose cell surface expresses pathogen associated molecular patterns [22, 23]. IL-6 binding to IL-6R promotes the transcription of acute phase proteins, T cell differentiation, and antibody production. It was approved to treat rheumatoid arthritis by the FDA in 2010 and has been used to treat juvenile systemic idiopathic arthritis, giant cell arteritis, and cytokine release syndrome after CAR-T therapy.

The rationale for using tocilizumab in COVID-19 is that IL-6 blockade could attenuate the hyperinflammatory response to SARS-CoV-2, which resembles cytokine storm. In 48 patients in Wuhan, China, IL-6 levels were correlated with the degree of SARS-CoV-2 viremia and an independent predictor of mortality [24]. Of 592 adult patients with severe COVID-19, those who received tocilizumab had lower all-cause mortality compared to those who received saline (16 vs 24%; relative risk 0.62 [0.31–1.22]) [25]. Serious adverse events occurred in 103 of 295 patients (34.9%) in the tocilizumab group and in 55 of 143 patients (38.5%) in the placebo group. A meta-analysis of 32 studies (29 cohort studies and 3 clinical trials) found no difference in mortality or frequency of adverse events [26].

A retrospective trial of 1827 patients with confirmed COVID-19 hospitalized between March 14, 2020, and April 23, 2020, reported transaminase elevations five times above the upper limit of normal as an independent predictor of mortality in patients who received an unspecified combination of lopinavir/ritonavir, hydroxychloroquine, remdesivir, and tocilizumab [27]. The most common adverse events attributed to tocilizumab are an increased incidence of opportunistic infections, reflecting immunosuppression, and clinically insignificant dyslipidemia [28].

In June 2021 the FDA issued an EUA for tocilizumab in patients 2 years or older hospitalized with COVID-19 and requiring supplemental oxygen who were also receiving corticosteroids [29]. The dose authorized is 12 mg/kg for those less than 30 kg and 8 mg/kg up to 800 mg for those heavier than 30 kg. The diluent is 0.9% or 0.45% saline, and the solution is infused over 1 h.

Sotrovimab

Sotrovimab is a recombinant IgG1-kappa made of 2 identical light and 2 identical heavy chains. Sotrovimab binds to a region in S2 that helps the host and virus membrane fuse. This region is conserved in SARS-CoV-2 across variants [30]. As of January 2022, sotrovimab is the only available monoclonal antibody believed effective against the omicron variant, illustrating the dependence of the efficacy of monoclonal antibodies on viral structure.

The FDA issued an EUA for a one-time infusion of 500 mg sotrovimab over 1 h on May 26, 2021, for non-hospitalized COVID-19 patients 12 years or older, heavier than 40 kg, and with at least one risk factor for progression of disease [16]. Sotrovimab is not approved or recommended for patients who require supplemental oxygen and is to be given within 10 days of symptom onset or 7 days after a positive COVID-19 test.

An interim analysis of an ongoing double-blinded multicenter trial, COMET-ICE, found that non-hospitalized patients with COVID-19 who received a one-time infusion of 500 mg sotrovimab were 85% relatively less likely (6% absolute risk reduction) to be hospitalized due to disease progression in the 29 days following the infusion than those who received saline [16]. This study included patients 18 years or older whose symptoms began within the last 5 days with at least 1 risk factor for disease progression (2). Seventy-three patients (17%) who received sotrovimab had an adverse event, compared to 85 (19%) who received saline. The most frequent were diarrhea (2%) and rash (1%). The type and location of the rashes were not detailed. Seven patients who received sotrovimab (2%) reported serious adverse events as opposed to 27 patients (6%) in the placebo group. The authors attributed most of these adverse events to disease progression. In addition, five patients (1%) who received sotrovimab reported infusion-related reactions compared with 6 (1%) who received saline. Reactions that occurred within 24 h of the infusion were considered related to the infusion. Infusion reactions were most commonly pyrexia, chills, dizziness, and dyspnea. There were no life-threatening reactions.

Another study compared the efficacy of sotrovimab in 546 hospitalized patients with SARS-CoV-2 to 0.9% saline and used the composite endpoint of length-of-stay and recurrent admissions and reported infusion-related adverse events in 18 patients (10%) who received sotrovimab and 14 patients (13%) who received saline. There is one report of anaphylaxis occurring 20 min after a 1-h sotrovimab infusion of 500 mg [31]. The patient improved after 2 doses of 0.3 mg intramuscular epinephrine.

Bamlanivimab and Etesevimab

Before the FDA approved the combination of bamlanivimab and etesevimab, it granted bamlanivimab an EUA as monotherapy based on interim results from the trial, BLAZE-1. Subsequent results from that same trial led to approval of the combination treatment.

Bamlanivimab, like sotrovimab, was initially isolated from the convalescent plasma of a SARS-COV-2 survivor. It contains 2 identical light and 2 identical heavy chains and binds to the receptor binding domain [32]. Binding to the RBD prevents SARS-CoV-2 from attaching to and then infecting human cells.

Etesevimab is a neutralizing antibody with 2 identical light and 2 identical heavy chains also isolated from the convalescent plasma of SARS-COV-2 survivors. It binds to a region in the RBD that overlaps with the region bamlanivimab targets. Data on etesevimab are limited to only trials involving etesevimab and bamlanivimab.

The FDA granted bamlanivimab an EUA based on interim results from the Blaze-1 clinical trial which reported that 2800 mg of bamlanivimab decreased viral load by a factor of 3.4 by day 11 of symptom onset compared to saline [33]. The FDA authorized bamlanivimab at a dose of 700 mg, which did not show a statistically significant reduction in viral load by day 11 of symptom onset. However, the results of the Blaze-1 trial determined that none of the 3 tested bamlanivimab monotherapy groups (700 mg, 2800 mg, 7000 mg) produced a significant decrease in viral load at day 11 of infection compared to placebo [32] and, based on this, the FDA revoked bamlanivimab's monotherapy EUA in February 2021. No serious adverse events or deaths were reported in any group. Fewer than 6% of patients experienced nausea or diarrhea, which were comparable to placebo groups.

The BLAZE-1 clinical trial also evaluated the combination of bamlanivimab and etesevimab, which did reduce viral load. In non-hospitalized patients with COVID-19 treatment with 2800 mg bamlanivimab and 2800 mg etesevimab infused over a total of 1 h reduced viral load at day 11 compared with saline placebo. Nausea was the most frequent adverse event, noted in 4 (3.6%) patients who received the combination and 6 (3.8%) who received saline. Immediately after the infusion, 2 patients who received the combination and 1 who received saline reported rash, itchiness, and facial flushing with no change in vital signs. Seven patients (1.4%) who received the combination and 5 who received saline (1.0%) reported serious adverse events. Of those who received the combination, 1% reported nausea, 1.2% rash, and 0.8% dizziness [34]. There was no description of the rash nor any discussion of infusion-related reactions.

In February 2021, the FDA issued an EUA for a one-time infusion of the combination of bamlanivimab 700 mg and

etesevimab 1400 mg to treat COVID-19 in non-hospitalized adults and children at high risk for progression to severe disease [13]. This combination therapy was also approved for post exposure prophylaxis for unvaccinated or immunosuppressed individuals who came into close contact with a COVID positive individual, ideally within 10 days of symptom onset. The EUA does not extend to hospitalized patients or anyone receiving supplemental oxygen. Bamlanivimab/etesevimab is given as an IV infusion in 0.9% saline. The FDA authorized dose for the combination for adults is bamlanivimab 700 mg and etesevimab 1400 mg, not the 2800 mg and 2800 mg used in the studies discussed above. The FDA cite an interim unpublished analysis for the lower dose. After the EUA, bamlanivimab 700 mg and etesevimab 1400 mg have been administered to roughly 800 patients across all clinical trials. There was 1 case of anaphylaxis that resolved after epinephrine and 16 infusion-related reactions.

Data for pediatric use come from an unplanned subgroup analysis of 125 children in Blaze-1. No children who received the combination therapy died or were hospitalized during treatment. The age range was from birth to 18, with most (74 patients) being 12–18 years old. The youngest child was 10 months old. Combination therapy is approved under EUA for pediatric patients less than 2 years of age who are hospitalized due to COVID.

Casirivimab and Imdevimab

In November 2020, the infusion or subcutaneous injection of casirivimab and imdevimab received EUA from the FDA for non-hospitalized COVID-19 patients over the age of 12 with immunosuppression or at high risk for disease progression, or for post exposure prophylaxis for immunosuppressed or unvaccinated patients at high risk for progression to severe disease. The FDA approved the dose of 600 mg casirivimab and 600 mg imdevimab [14]. This differs from the initially authorized dose of 1200 mg of casirivimab and 1200 mg of imdevimab, reflecting a phase 3 study that showed similar efficacy at the lower dose. The combination therapy uses either 0.9% saline or 5% dextrose in water as its diluent [35]. This therapy is not offered under the EUA to patients hospitalized due to SARS-COV-2 or who are on oxygen currently because there are no data on these groups.

Casirivimab and imdevimab are neutralizing monoclonal antibodies. Each is made up of two identical light and two identical heavy chains. Both antibodies bind to the RBD, but they target different regions of the RBD, like the combination of bamlanivimab and etesevimab. They were initially identified from convalescent plasma obtained from COVID-19 survivors. Casirivimab and imdevimab have been administered in dosages up to 4000 mg without any observed dose limiting toxicity.

As per the FDA's EUA, 16,000 patients have received the combination therapy (13,500 intravenous infusions, 2500 subcutaneous injection). Ten patients out of 4,206 who received the infusion had an infusion reaction involving more than local irritation. The infusion had to be stopped in 3 because of urticaria, dyspnea, chest tightness, and vomiting. One patient had anaphylaxis. The COV-2093 trial evaluated the safety of subcutaneous injection involving 600 mg of casirivimab and imdevimab and reported site reactions in 12% of casirivimab and imdevimab group (approximately 87 people) compared to 4% of placebo (approximately 9 people) [14]. Repeat dosing produced injection site reactions in 35% of the casirivimab and imdevimab group (252 people) compared to 16% in the placebo group (38 people).

Vaccines

The goal of a vaccine is to develop longstanding immunity without exposure to the full disease. The existence of variants complicates this goal. Vaccines stimulate the production of antibodies that interact with a specific part of the virus (the epitope). Viruses may be able to mutate away from that structure. Vaccines may also cause "original antigenic sin," a process where subsequent infections with similar virus strains preferentially boost the antibody response against the original strain leading to a paradoxically weaker response to the second strain [36, 37]. We refer the reader to [38] for a review of the development, distribution, and mechanism of action of SARS-CoV-2 vaccines. As of this writing, the Moderna, Pfizer, Johnson & Johnson, and Novavax (a protein vaccine not discussed here) are approved by the FDA.

Protein Vaccines

Protein vaccines against COVID-19 contain the soluble SARS-CoV-2 viral spike protein with adjuvants added to the formulation to bolster robust humoral and cellular immunogenicity against SARS-CoV-2. Protein vaccines are often poorly immunogenic unless they have immunogenic adjuvants [39].

SCB-2019

SCB-2019 is a recombinant protein vaccine that contains antigenic subunits of the S protein with adjuvants AS03 (α-tocopherol, squalene and polysorbate 80 in an oil-in-water emulsion) or CpG/Alum (a toll-like receptor agonist complexed with aluminum).

Of 151 healthy volunteers who received the SCB-2019 vaccine almost half reported local site reactions, more frequent with the AS03 adjuvant (44–69%) than the CpG/Alum adjuvant (6–44%) or no adjuvant (3–13%). Systemic adverse

events were more frequent in those adults younger than 30 (38%) than in older adults (17%) [40]. In the larger Phase 2/3 SPECTRA trial, mild-to-moderate injection site pain was reported more by those who received the vaccine ($n=6215$) than the placebo ($n=6104$) after the first (35.7%; 287 of 803 vs 10.3%; 81 of 786) or second dose (26.9%; 189 of 702 vs 7.4%; 52 of 699). The proportion of other solicited local and systemic adverse events were similar between the groups [41].

Nucleic Acid Vaccines

DNA vaccines introduce viral DNA into host cells that codes for a protein or proteins integral to viral function (for SARS-CoV-2 usually the S protein). Without integrating itself into the host DNA, the sequence is transcribed into mRNA and translated into the amino acid sequence for the S protein, which is subsequently expressed on the surface of host cells inducing an immune response [42]. mRNA vaccines directly inject mRNA into the host cytoplasm, bypassing the introduction of DNA to the nucleus and the need for transcription.

GLS-5300 is a DNA vaccine that encodes the S protein of MERS-CoV, the coronavirus that causes Middle East Respiratory Syndrome (MERS). An open label phase I/IIa trial evaluating GLS-5300 against SARS-CoV-2 reported no serious adverse events up to 4 weeks after injection but the abstract did not specify the number of people enrolled and no full-text was available from the publisher web site, WHO web site or PubMed, only a meeting abstract [43].

INO-4800 is a DNA vaccine that encodes the SARS-CoV-2 S protein. A phase 1 clinical trial INO-4800 reported 100% safety and tolerability in 38 healthy individuals [44]. The follow-up phase 2 trial reported results in a preprint 1 year ago [45] with, to date, no associated peer-reviewed publication. The preprint reported that nearly 1 in 2 recipients experienced local site irritation, pain, or swelling, but reported no serious adverse events.

Johnson & Johnson (Ad26.COV2.S) Vaccine

The Johnson & Johnson COVID-19 Vaccine (Ad26.COV2.S) confers passive immunity against SARS-CoV-2 by raising antibodies against the S protein. It uses recombinant human adenovirus serotype 26 (Ad26) to introduce a DNA sequence encoding the entire S protein. The DNA sequence is stabilized with furin cleavage-site mutations, modified to code for 2 consecutive proline substitutions in the eventual protein, and modified to remove its ability to replicate by deleting the E1 gene [46, 47]. Ad26-vector vaccines are generally considered safe and effective constructs, having been used for RSV, Zika, and HPV vaccines [48]. The Sputnik V vaccine also uses Ad26.

The Johnson & Johnson COVID-19 Vaccine (Ad26.COV2.S) is the third vaccine to receive EUA by the FDA for the prevention of COVID-19 in patients 18 years of age and older [49]. The most reported symptoms from clinical trials were pain at the injection site (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.1%), and nausea (14.2%) [50]. The frequency of serious adverse events was 0.4% for both vaccine and control groups. Embolic and thrombotic events occurred at a frequency of 0.06% in the vaccine group and 0.05% in the placebo group. Six patients who received the vaccines developed appendicitis in the following 28 days, compared with 5 who received the placebo. There were 3 serious adverse events in the vaccine group that the FDA considered as likely associated with the vaccine: a hypersensitivity reaction, pain at injection site evaluated for brachial neuritis, and systemic reactogenicity. Angioedema occurred in 0.2% of those in the vaccine group in contrast to 0.1% in the placebo group, urticaria in 8 vs 3 individuals and tinnitus in 6 vs 0, respectively. Cases of urticaria were deemed plausibly associated with the vaccine.

Use of Ad26.COV2.S was paused after 6 cases of cerebral venous sinus thrombosis were reported in the first two months after approval [51]. The CDC reported an additional 17 cases of thrombosis with thrombocytosis in 8 million doses administered [52]. The pause was lifted 10 days later.

mRNA Vaccines

The Pfizer-BioNTech (BNT162b2) and the Moderna (mRNA-1273) vaccines confer passive immunity against SARS-CoV-2 by raising antibodies against the Spike (S) protein. Both vaccines deliver mRNA encoding the entire S protein with 2 equal proline substitutions for stability. An equal amino acid substitution is one that exchanges one amino acid for another biochemically similar one.

Possible adverse effects to mRNA vaccines include the generation of autoantibodies, adverse reactions to adjuvants, or diluents, and induction of type I interferon responses. Extracellular RNA may impact endothelial processes [53], promoting coagulation [54, 55] and vascular permeability [56].

The mRNA is packaged into lipid nanoparticles (LNPs) and stabilized with polyethylene glycol. After intramuscular injection, antigen presenting cells (APCs) internalize the LNPs and translate the mRNA into the S protein. These APCs then migrate to lymph nodes where they present (express on their cell surface) the S protein to B and T cells. The B cells produce antibodies to the Spike protein, which they now perceive as an antigen. The T cells play a role in passive immunity [57].

mRNA vaccines are not infectious and carry no risk of insertional mutagenesis [58]. LNPs, originally designed to ferry xenobiotics, allow the mRNA to infect (enter) the cell,

which it cannot do on its own. At low pH, LNPs are positively charged, attracting the RNA whose phosphate groups make RNA negatively charged. The LNP-mRNA complex is neutral and is taken up by endocytosis into the cell. At physiologic pH the LNP is neutral. Thus, once inside the cell, the LNP and mRNA dissociate, leaving mRNA transcript in the APC cytoplasm that is indistinguishable from the APCs own mRNA. After a few rounds of translation, the LNP and mRNA are destroyed, and the APC stops manufacturing the S protein [59].

Pfizer-BioNTech (BNT162b2) Vaccine

On December 11, 2020, the COVID-19 Pfizer-BioNTech (BNT162b2) vaccine became the first to receive EUA by the US Food and Drug Administration (FDA) for the prevention of COVID-19 in patients 16 years and older [60], later extending approval for children 5 years and older [61, 62]. The most reported symptoms from clinical trials across age groups after the first and second doses were: pain at injection site (78.4% and 73.3%, respectively), fatigue (42.9% and 53.6%), headache (35.3% and 45.0%), muscle pain (17.0% and 28.2%), and chills (12.1% and 27.0%) [63].

During the clinical trial that supported the EUA, those who received the vaccine had more adverse events than those who received the placebo, although these events were almost entirely mild and self-limited, such as lymphadenopathy in the head and neck. There were 4 cases of Bell's palsy in the vaccine group (and none in the placebo group or in the 5 to 11, 12 to 15 age groups), a frequency that is not greater than the baseline frequency in that population. Serious events were reported in 0.6% of patients in the vaccine group and 0.5% in the placebo group, most frequently appendicitis (7 vs 2 cases), acute myocardial infarction (3 vs 0 cases) and cerebrovascular accident (3 cases vs 1 case). No serious adverse events were associated with the vaccine in ages 5 to 15 [63].

Moderna (mRNA-1273) Vaccine

On December 18th, 2020, the Moderna COVID-19 Vaccine (mRNA-1273) became the second vaccine to receive EUA by the FDA to prevent COVID-19 infection in patients 18 years of age and older [64]. The most reported symptoms after the first and second doses were pain at the injection site (83.7% and 88.7%, respectively), fatigue (37.2% and 65.2%), headache (32.7% and 58.5%), muscle pain (22.7% and 57.6%), and arthralgia (16.6% and 42.6%) [65].

Those who received the vaccine reported more adverse events than those who received the placebo, usually lymphadenopathy in the arm and neck. There were 3 reported cases of Bell's palsy (one a serious adverse event) in the vaccine group and 1 in the placebo group. The most frequent serious adverse events more frequent in the vaccine group were myocardial infarction (5 vs 3 cases), cholecystitis (3 vs 0 cases), and nephrolithiasis (3 vs 0 cases). The FDA considered 1 case of intractable nausea and vomiting and 2 cases of facial swelling (both in individuals with previous cosmetic injections) as possibly associated with the vaccine.

Serious Adverse Events Post-Emergency Use Authorization

The Pfizer-BioNTech and Moderna vaccines have been associated with myocarditis [66–77], and anaphylaxis [78–84]. The Johnson & Johnson vaccine has been associated with thrombosis with thrombocytopenia syndrome (TTS) and Guillain-Barré syndrome (GBS). Data supporting these associations come from the Vaccine Adverse Event Reporting System (VAERS). VAERS surveys a larger group than do clinical trials, allowing VAERS to detect rarer events or events in populations the clinical trials did not study.

Myocarditis

Myocarditis or pericarditis typically develop within 7 days of receiving the Pfizer-BioNTech or Moderna vaccines (74% of cases for the 1st dose, 90% for the 2nd) if they are going to develop [85]. Of the 1991 cases reported to VAERS between December 14, 2020, and August 31, 2021, following at least 1 dose of the Pfizer-BioNTech or Moderna vaccines, in individuals older than 12 years of age, 1626 met the CDC's definition of probable or confirmed myocarditis: 1,136 (70%) after the Pfizer-BioNTech vaccine and 490 (30%) after the Moderna vaccine. Of these 1626 cases, 82% were in men, 73% occurred in individuals 12 to 29 years of age, and 82% were after the second dose [74].

Pfizer and Moderna vaccines increase the risk of myocarditis. The average estimated rate across all age groups of myocarditis is 5.4 cases per 1,000,000 vaccine doses for Pfizer and 3.4 per 1,000,000 vaccine doses for Moderna. This increase is less than the risk of developing myocarditis from COVID-19 (relative risk: 2 [95% CI, 1.44–2.65, vaccinated] vs 15 [95% CI, 11.09–19.8, unvaccinated]) [86, 87]. For the Pfizer vaccine, myocarditis was most common during the 7 days after the second Pfizer-BioNTech dose for males and females aged 16–17, at 105.86 [95% CI, 91.65–122.27] and 10.98 [95% CI, 7.16–16.84] cases per million doses, respectively. The baseline rates for myocarditis in those age groups are 1.34 [95% CI, 1.05–1.72] and 0.42 [95% CI, 0.27–0.66] *cases* per million persons, respectively. For the Moderna vaccine, myocarditis was most common during the 7 days after the second dose for males 18 to 24 years at 56.31 cases per million doses [95% CI, 47.08–67.34], compared to the baseline rate of 1.76 [95% CI, 1.58–1.98] cases per million persons and females aged 25 to 29 years at 8.22

[95% CI, 5.03–13.41] cases per million doses, compared to the baseline rate of 0.48 cases per million persons [95% CI, 0.35–0.65] [74]. We provide expected values that we calculated for comparison, although the expected values are cases per person and reported values cases per *vaccine dose*. A simple and perhaps simplistic conversion is to multiply the rate per dose by the number of doses. Further complicating comparison, Moderna was authorized later than Pfizer leading to possible confounding by the varying inflammatory effects of different SARS-CoV-2 variants.

Myocarditis after the Pfizer-BioNTech vaccine has also been reported in males aged 12 to 17. At the time of preparation of this manuscript, no data on the Moderna vaccine were available. Out of 8,674,378 administered doses, 16 associated cases of myocarditis were reported to VAERS. The median age was 10 years (IQR, 9–11 years). Most cases (67%) occurred in males. The median time between receiving the vaccine and symptoms starting was 2 days. The incidence of myocarditis during the 7 days after the second dose of the Pfizer-BioNTech in those aged 5 to 11 was 4.3 cases per million administered doses in males and 2.0 in females. The background incidence of myocarditis in this age group is 0.2 to 1.9 per million persons [77, 87].

In patients 30 years or younger who were ultimately diagnosed with vaccine-associated myocarditis, 89% reported chest pain (including pressure or discomfort), 98% had an elevated troponin level, and 72% had an abnormal EKG. Cardiac MRI was abnormal 72% of the time [71]. Bozkurt et al. reported similar findings in a case series from 61 patients 14 to 70 years old with myocarditis in Israel, Italy, Spain, and the USA after receiving the Pfizer-BioNTech or Moderna vaccines [77]. Of those patients, 98% were male. All had chest pain, troponin elevation, and abnormal cardiac MRI (most commonly late gadolinium enhancement). ECG changes were seen in 87% of patients with ST elevations being the most common finding. An abnormal echocardiogram was reported in 39% with 15% having LVEF < 50% [77].

A case series by Dionne et al. reported similar clinical presentations in children ages 12 to 18 [76]. Out of 15 patients (93% male) hospitalized with myocarditis within 30 days of receiving the Pfizer-BioNTech vaccine, 100% had chest pain and elevation in troponins. Diffuse ST elevations were seen in 9 (60%) of the patients at time of hospital admission. Decreased LVEF (44% to 53%) was seen in 20% of patients and 12 had late gadolinium enhancement.

Most reported myocarditis cases resolved either spontaneously or with the standard interventions for myocarditis. Treatments included non-steroidal anti-inflammatory drugs, colchicine, aspirin, glucocorticoids, intravenous immunoglobulin, beta blockers, or angiotensin-converting enzyme inhibitors [74, 76, 77]. Vasoactive medications, intubation or mechanical ventilation have been reported once [76].

The increased incidence of myocarditis in young adult men is not unique to mRNA vaccines for COVID. A similar association has been reported for the smallpox and influenza vaccines [88, 89]. The biological mechanism underlying this association is not fully understood. Perhaps the antibodies the immune system makes have off-target effects (molecular mimicry). The mRNA could have off target effects or unanticipated immunogenicity.

Anaphylaxis

Data in December 2020 estimated the incidence of anaphylaxis to the first dose of the Pfizer-BioNTech vaccine as 4.7 cases per 1,000,000 doses [78]. Of these, 90% were female, 81% had a history of allergies and 86% had symptom onset within 30 min of vaccination. The estimated incidence of anaphylaxis to the first dose of the Moderna vaccine was 2.5 per 1,000,000 doses. All confirmed cases occurred in females, with 90% having a previous history of allergies and 90% occurring within 30 min of vaccine administration [83]. Most anaphylactic reactions occurred after the first dose [84]. For comparison, incidence of anaphylaxis to succinylcholine, vancomycin, and piperacillin/tazobactam have been estimated at 1.11, 0.57, and 0.35 per 1,000,000 administrations, respectively [90].

The trigger for anaphylaxis after administration of the Pfizer-BioNTech or Moderna mRNA vaccines is not yet clear. It may involve the vaccine excipient. Both use polyethylene glycol (PEG) 2000 to stabilize the lipid nanoparticles [91, 92]. Skin prick testing in an individual with an anaphylactic reaction after receiving the Pfizer-BioNTech vaccine showed reactivity to PEG [81]. Non-IgE mediated responses to the lipid or PEG are also possible [93].

Thrombosis with Thrombocytopenia Syndrome (TTS)

TTS is a generalization of heparin-induced thrombocytopenia. It is between 10 and 100 times more prevalent after COVID vaccinations than in the general population [94]. Cases of TTS were reported in individuals who received the Oxford-AstraZeneca vaccine (ChAdOx1 nCoV-19) 5–16 days earlier. These patients raised antibodies against platelet factor 4 but had not received heparin [96].

The Oxford-AstraZeneca vaccine is a recombinant chimpanzee adenoviral vector that encodes the S protein of SARS-CoV-2 [95]. When TSS was also reported in individuals who received the Johnson & Jonson vaccine (a human adenovirus vector vaccine), an association between the adenovirus vector and the formation of anti-platelet factor 4 antibodies was proposed [96]. The Oxford-AstraZeneca and Johnson & Johnson vaccines are both DNA vaccines that use adenovirus as a vector. The Oxford-AstraZeneca vaccine is not approved for use in the United States but is in many parts

of the world. The Johnson & Johnson vaccine has an emergency use authorization by the FDA. Between March and August 2021, 54 valid cases (out of 14,080,087 vaccination administrations) were reported, a case-event rate of 3.8 cases per million Johnson & Johnson COVID-19 vaccine doses. Of these 54 cases, 8 (14.8%) resulted in death (0.6 deaths due to TTS per million vaccine doses). Most cases (68.5%) occurred in women with 48.1% of total cases occurring in women ages 18 to 49. The highest incidence occurred in those ages 30 to 39 (10.6 cases per million vaccine doses), followed by those 40 to 49 years of age (9.0 cases per million vaccine doses). The death rate due to TSS was 1.9 deaths per million vaccine doses in women ages 30 to 39 and 1.8 in women 40 to 49 years of age. Among men, the highest incidence and mortality was seen in ages 40 to 49 with 4.3 cases per million vaccines doses and 0.7 deaths per million vaccine doses, respectively [97].

The mainstay of treatment of TTS is 2 gm/kg IVIG given over 2–5 days and anticoagulation, avoiding heparin or Vitamin K antagonists. Plasma exchange can be used in those who do not respond to IVIG.

Safety of Boosters

A chart review aided by natural language processing of 47, 999 persons who received three doses of mRNAs vaccines (57.3% women, median [IQR] age 67.4 [52.5–76.5]) found no increased risk of pericarditis, myocarditis, anaphylaxis, or cerebral venous sinus thrombosis after the third dose; however, about 10% more individuals reported fatigue, lymphadenopathy, headache, arthralgias, and myalgias after the third dose than the second [98].

Vaccines Developed in China

Of the four vaccines made in China, CoronoVac and Sinopharm are the most common, followed by CanSinBio and another produced jointly by Anhui Zhifei Longcom Biopharmaceutical and the Chinese Academy of Sciences. China's CoronaVac and Sinopharm vaccines, used in China as well as 54 other countries, account for almost half of the 7.3 billion COVID-19 vaccine doses delivered globally [99]. CoronaVac and Sinopharm vaccines are based on an inactivated form of SARS-CoV-2. CanSinBio and an unnamed one by produced by Anhui Zhifei Longcom Biopharmaceutical and the Chinese Academy of Sciences use adenovirus to deliver immunogenic parts of the Spike protein [100].

CoronaVac (also called SinoVac)

In a Phase 1 trial of healthy adults in China, the incidence of adverse effects ranged from 29 to 38%, depending on dose used, 3 µg or 6 µg, compared to 8% of those who received placebo. In the phase 2 trial, adverse effects ranged from 33 to 35%, depending on the dose, compared to 22% of those who received the placebo [101]. The most reported adverse-event was injection-site pain. Most reactions were mild (grade 1) and resolved within 48 h. The authors reported no serious adverse events within 28 days of vaccination. One case of urticaria 48 h after a patient received the 6 µg injection was reported and the patient recovered after being treated with chlorpheniramine and dexamethasone with no recrudescence after the second dose of vaccine. Ten (7%) of 143 participants in phase 1 had a clinically significant increase of laboratory indicators (transaminase elevations, CK elevation, or blood or protein in urine) in the first 3 days after receiving the vaccination.

An interim analysis of a phase III trial in the United Arab Emirates and Bahrain reported transient and self-limiting grade 1 or 2 reactions in about half of those who received the vaccine or the placebo (48% and 50%, respectively) and no severe events definitely related to the vaccine [102]. A double-blind randomized placebo-controlled trial of 10,128 participants in Turkey reported adverse events in 1259 (18.9%) participants in the vaccine group ($n=6646$) and 603 (16.9%) in the placebo group ($n=3470$) with no fatalities or grade 4 adverse events. The most common systemic adverse event was fatigue (546 [8.2%] participants in the vaccine group and 248 [7.0%] in placebo group). Pain at the injection site was the most frequent local adverse event (157 [2.4%] vs 40 [1.1%], respectively) [103].

Sinopharm

Like CoronaVac, the SinoPharm vaccine is an inactivated virus harvested from Vero cells inoculated with a specific strain of SARS CoV-2. CoronaVac uses the CN02 strain and SinoPharm uses the WIV04 strain [104]. A study in Hungary of 3,740,066 participants.

quantifying the efficacy of 5 COVID vaccines reported that SinoPharm was 68% effective, but many participants mixed and matched vaccines and adverse events were not recorded [105]. An ecological study of 663, 602 residents in Argentina reported a higher rate of reinfection after SinoPharm and also did not record adverse events [106].

CanSinBio

CanSinBio is a DNA vaccine like Johnson & Johnson. In a phase I trial of 130 participants in Wuhan, China, within 7 days after vaccination, adverse events occurred in approximately 70% of those who received the vaccine intramuscularly and 65% of those who received it via nebulizer. The most common adverse events reported 7 days after the first or booster vaccine were fever (62 patients, 48%), fatigue (40 patients, 31%), and headache (46 patients, 35%) [107].

Anuhui Zhifei Longcom Zifivax (RBD-Dimer, ZF2001)

ZF2001 contains a tandem-repeat dimeric form of the receptor-binding domain of SARS-CoV-2 S protein as the antigen and aluminum hydroxide as an adjuvant. It works by developing immunity to the receptor binding domain of the S protein [108]. The incidence of local reactions in the ZF2001 group was 18.8% and systemic reactions was 25.1%. Serious adverse events were reported by 199 patients (1.4%) in the ZF2001 group and 264 patients (1.8%) in the placebo group. 4 patients (2 in the ZF2001 group and 2 in the placebo group) developed hypersensitivity reactions. All symptoms resolved after medical treatment without sequelae. No cases of antibody-dependent enhancement or vaccine-enhanced disease were confirmed. The second and third vaccine injections did not further increase the incidence of adverse reactions.

Sputnik V and Sputnik Light

Sputnik V (Gam-COVID-Vac) and Sputnik Light are non-replicating adenovirus viral vector vaccines developed by the Gamalia Institute of Epidemiology and Microbiology in Moscow, Russia. It is a two-dose COVID-19 vaccine designed to generate antibodies against the S protein. The first dose uses Ad5. The second dose, given 3 weeks later, uses Ad26. Ad26 elicits a less robust T cell response than Ad5 [109] but escapes immunity to Ad5 [110].

Sputnik Light is the first dose of Sputnik V. It was created to facilitate distribution to countries with widespread infection that need to quickly vaccinate. Sputnik Light can be stored at 2–8 °C, compared to Sputnik V, which must be stored at below –18 °C. Sputnik Light can be used as the third (booster) dose for those who received Sputnik V. The clinical trials for the vaccines reported safety and efficacy, but the adverse events were collected through self-reporting diaries and not explicitly presented [111]. In another trial, there were no serious adverse reactions reported, with the most common being pain at the injection site (7/110) and a flu-like symptom (72/110). Eleven of the 110 participants had self-resolving clinically insignificant laboratory abnormalities, including elevations in transaminases, erythrocyte sedimentation rate, and lactate dehydrogenase as well as both leukopenia and leukocytosis and neutropenia [112].

An analysis of 11, 515 self-reports of adverse events from Russian users who posted on the social media platform Telegram reported pain (47%) fever (46%), fatigue (33%), and headache (25%) to be the most frequently mentioned events [113]. Women reported more adverse events than men ($P < 0.001$), more AEs occurred after the first dose than the second dose ($P < 0.001$), and the number of AEs decreased with age ($P < 0.001$). The authors assessed gender based on the gender listed in each user's profile.

An analysis of self-reports from 3236 Iranian healthcare workers in Mazandaran, Iran, who were vaccinated with Sputnik V (mean age 39.32, 61.2% women) reported pain (56.9%), fatigue (50.9%), body pain (43.9%), headache (35.7%), fever (32.9%), joint pain (30.3%), chills (29.8%), and drowsiness (20.3%) as the most common side effects [114]. No cases of myocarditis or pulmonary embolus were reported. A study of self-reports from 503 healthcare workers in Birjand, Iran, found muscle pain, fatigue, and fever to be the most common adverse events after the first dose of Sputnik V [115], occurring in 48% of those who received the vaccine, although the study did not report the frequency of each symptom individually.

A study from Buenos Aires, Argentina evaluated adverse events in healthcare workers (median age 35 years, 67% females) that received Sputnik V. The most reported adverse events were pain at the injection site (57%), redness and swelling, (11%) new or worsened muscle pain (58%), fever (40%), and diarrhea (5%). Thirty-four participants (5%) had serious adverse (facial swelling, difficulty breathing) events requiring emergency treatment and, for one participant, hospitalization. There have been no reports of thromboembolic events from Russian health authorities or from those other nations using Sputnik V [116].

Conclusion

The adverse effects from vaccines against COVID-19 resemble those from previous vaccines in type and frequency, including a slight increase in the risk of myocarditis for young males. Monoclonal antibodies and convalescent plasma have similar infusion-related reactions. They also have idiosyncratic side effects and variable and varying efficacy, reflecting their specificity for certain S protein sequences. Safety data on recombinant protein infusions are not available and the paucity of publications suggests little ongoing development.

Acknowledgements We thank the administrative staff at Boston Children's Hospital and Weill Cornell Medicine for their support.

Funding Sudeh Izadmehr is supported by the Loan Repayment Program (National Center for Advancing Translational Scientists, National Institutes of Health) and the T32 Cancer Biology Training Program (5T32CA078207, National Cancer Institute, National Institutes of Health). Michael A. Chary is supported by the Loan Repayment Program (National Institute for Drug Abuse, National Institutes of Health).

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Boehmer TK, Kompaniyets L, Lavery AM, Hsu J, et al. Association between COVID-19 and myocarditis using hospital-based administrative data - United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep. 2021;70(35):1228–1232. https://doi.org/10.15585/mmwr.mm7035e5
2. Kang Y, Chen T, Mui D, Ferrari V, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Heart. 2020;106(15):1132–41. https://doi.org/10.1136/heartjnl-2020-317056.
3. Khubchandani J, Sharma S, Price JH, Wiblishauser MJ, et al. COVID-19 vaccination hesitancy in the United States: a rapid national assessment. J Community Health. 2021;46(2):270–7. https://doi.org/10.1007/s10900-020-00958-x.
4. Meo SA, Bukhari IA, Akram J, Meo AS, et al. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci. 2021;25(3):1663–1669. https://doi.org/10.26355/eurrev_202102_24877
5. Chary MA, Barbuto AF, Izadmehr S, Hayes BD, Burns MM. COVID-19: therapeutics and Their Toxicities. J Med Toxicol. 2020;16(3):284–94. https://doi.org/10.1007/s13181-020-00777-5.
6. Huang Y, Yang C, Xu XF, et al. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141–9. https://doi.org/10.1038/s41401-020-0485-4.
7. Zheng K, Bantog C, Bayer R. The impact of glycosylation on monoclonal antibody conformation and stability. MAbs. 2011;3(6):568–76. https://doi.org/10.4161/mabs.3.6.17922
8. Pilot clinical trial in China to test UBC researcher's findings as a targeted therapy for COVID-19 - UBC Faculty of Medicine. 2020. https://www.med.ubc.ca/news/pilot-clinical-trial-in-china-to-test-ubc-researchers-findings-as-a-targeted-therapy-for-covid-19/. Accessed 22 Mar 2020
9. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211(1):80–90. https://doi.org/10.1093/infdis/jiu396.
10. Senefeld JW, Johnson PW, Kunze KL, Bloch EM, et al. Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study. PLoS Med. 2021;18(12):e1003872. https://doi.org/10.1371/journal.pmed.1003872
11. Breedveld FC. Therapeutic monoclonal antibodies. Lancet. 2000;355(9205):735–40. https://doi.org/10.1016/s0140-6736(00)01034-5.
12. U.S. Food and Drug Administration. Fact sheet for healthcare providers Emergency Use Authorization (EUA) for Sotrovimab. https://www.fda.gov/media/149534/download. Accessed 6 Jan 2022
13. U.S. Food and Drug Administration. Fact sheet for health care providers emergency use authorisation (EUA) of bamlanivimab and etesevimab authorized use treatment. 2022. from https://www.fda.gov/media/145802/download. Accessed 18 Jan 2022
14. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab).2021. https://www.fda.gov/media/145611/download. Accessed 6 Jan 2022
15. Taylor PC, Adams AC, Hufford MM, de la Torre I, et al. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol. 2021;21(6):382–93. https://doi.org/10.1038/s41577-021-00542-x.
16. Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med. 2021;385(21):1941–50. https://doi.org/10.1056/NEJMoa2107934.
17. Brennan FR, Morton LD, Spindeldreher S, Kiessling A, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. MAbs. 2010;2(3):233–55. https://doi.org/10.4161/mabs.2.3.11782
18. Tang CH, Hsu CJ, Fong YC. The CCL5/CCR5 axis promotes interleukin-6 production in human synovial fibroblasts. Arthritis Rheum. 2010;62(12):3615–24. https://doi.org/10.1002/art.27755.
19. Yang B, Fulcher JA, Ahn J, Berro M, et al. Clinical characteristics and outcomes of coronavirus disease 2019 patients who received compassionate-use leronlimab. Clin Infect Dis. 2021;73(11):e4082–9. https://doi.org/10.1093/cid/ciaa1583.
20. Agresti N, Lalezari JP, Amodeo PP, Mody K, et al. Disruption of CCR5 signaling to treat COVID-19-associated cytokine storm: case series of four critically ill patients treated with leronlimab. J Transl Autoimmun. 2021;4:100083. https://doi.org/10.1016/j.jtauto.2021.100083
21. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45. https://doi.org/10.1016/S0140-6736(21)00676-0.
22. Schmidt-Arras D, Rose-John S. IL-6 pathway in the liver: from physiopathology to therapy. J Hepatol. 2016;64(6):1403–15. https://doi.org/10.1016/j.jhep.2016.02.004.
23. Kishimoto T. Interleukin-6: from basic science to medicine–40 years in immunology. Annu Rev Immunol. 2005;23:1–21. https://doi.org/10.1146/annurev.immunol.23.021704.115806.
24. Chen X, Zhao B, Qu Y, Chen Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. Clin Infect Dis. 2020;71(8):1937–42. https://doi.org/10.1093/cid/ciaa449.
25. Rosas IO, Bräu N, Waters M, Go RC, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med. 2021;384(16):1503–16. https://doi.org/10.1056/NEJMoa2028700.
26. Chen CX, Hu F, Wei J, Yuan LT, et al. Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019 (COVID-19). Leukemia. 2021;35(6):1661–70. https://doi.org/10.1038/s41375-021-01264-8.
27. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, et al. Abnormal liver tests in COVID-19: a retrospective observational cohort study of 1,827 patients in a major U.S. hospital network. Hepatology. 2020;72(4):1169–1176. https://doi.org/10.1002/hep.31487
28. Khiali S, Khani E, Entezari-Maleki T. A comprehensive review of tocilizumab in COVID-19 acute respiratory distress syndrome. J Clin Pharmacol. 2020;60(9):1131–46. https://doi.org/10.1002/jcph.1693.
29. U.S. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for actemra (tocilizumab). 2021. https://www.fda.gov/media/150320/download. Accessed 12 Dec 2022.
30. Descotes J. Immunotoxicity of monoclonal antibodies. MAbs. 2009;1(2):104–11. https://doi.org/10.4161/mabs.1.2.7909
31. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 2022;22(5):622–635. https://doi.org/10.1016/S1473-3099(21)00751-9

32. Gottlieb RL, Nirula A, Chen P, Boscia J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2021;325(7):632–44. https://doi.org/10.1001/jama.2021.0202.
33. Chen P, Nirula A, Heller B, Gottlieb RL, et al. SARS-CoV-2 Neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. 2021;384(3):229–37. https://doi.org/10.1056/NEJMoa2029849.
34. Dougan M, Nirula A, Azizad M, Mocherla B, et al. N Engl J Med. 2021;385(15):1382–92. https://doi.org/10.1056/NEJMoa2102685.
35. Weinreich DM, Sivapalasingam S, Norton T, Ali S, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med. 2021;385(23):e81. https://doi.org/10.1056/NEJMoa2108163.
36. Davenport FM, Hennessy AV, Francis T Jr. Epidemiologic and immunologic significance of age distribution of antibody to antigenic variants of influenza virus. J Exp Med. 1953;98(6):641–56. https://doi.org/10.1084/jem.98.6.641.
37. Perlman S, Masters PS. Coronaviridae: the viruses and their replication. In: Howley PM, Knipe DM, editors. Fields' virology: emerging viruses. Lippincott Williams & Wilkins; 2020. p. 410–48.
38. Patel R, Kaki M, Potluri VS, Kahar P, et al. A comprehensive review of SARS-CoV-2 vaccines: Pfizer, Moderna & Johnson & Johnson. Hum Vaccin Immunother. 2022;18(1):2002083. https://doi.org/10.1080/21645515.2021.2002083.
39. Lee S, Nguyen MT. Recent advances of vaccine adjuvants for infectious diseases. Immune Netw. 2015;15(2):51–7. https://doi.org/10.4110/in.2015.15.2.51.
40. Richmond P, Hatchuel L, Dong M, Ma B, et al. Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: a phase 1, randomised, double-blind, placebo-controlled trial. Lancet. 2021;397(10275):682–94. https://doi.org/10.1016/S0140-6736(21)00241-5.
41. Bravo L, Smolenov I, Han HH, Li P, et al. Efficacy of the adjuvanted subunit protein COVID-19 vaccine, SCB-2019: a phase 2 and 3 multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2022;399(10323):461–72. https://doi.org/10.1016/S0140-6736(22)00055-1.
42. Mascellino MT, Di Timoteo F, De Angelis M, Oliva A. Overview of the main anti-SARS-CoV-2 vaccines: mechanism of action, efficacy and safety. Infect Drug Resist. 2021;31(14):3459–76. https://doi.org/10.2147/IDR.S315727.
43. Roberts CC, Oh MD, Kim ES, Jeong M, et al. Phase I-IIA study of GLS-5300 vaccine for Mers-Cov: preliminary results demonstrate B and T cell immune response elicited in lower-dose 2- and 3-vaccination intradermally administered regimens. Abstract 955 in 2020 ASGCT Annual Meeting Abstracts. Mol Ther. 2020;28(4):416–417
44. Tebas P, Yang S, Boyer JD, Reuschel EL, et al. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: a preliminary report of an open-label, Phase 1 clinical trial. EClinicalMedicine. 2021;31:100689. https://doi.org/10.1016/j.eclinm.2020.100689
45. Mammen MP, Tebas P, Agnes J, Giffear M, et al. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: a preliminary report of a randomized, blinded, placebo-controlled, Phase 2 clinical trial in adults at high risk of viral exposure. medRxiv.2021.05.07.21256652. https://doi.org/10.1101/2021.05.07.21256652
46. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med 2021;384(19):1824–1835. https://doi.org/10.1056/NEJMoa2034201
47. Bos R, Rutten L, van der Lubbe JEM, Bakkers MJG, Hardenberg G, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. NPJ Vaccines. 2020;28(5):91. https://doi.org/10.1038/s41541-020-00243-x.
48. Custers J, Kim D, Leyssen M, Gurwith M, et al. Vaccines based on replication incompetent Ad26 viral vectors: standardized template with key considerations for a risk/benefit assessment. Vaccine. 2021;39(22):3081–101. https://doi.org/10.1016/j.vaccine.2020.09.018.
49. U.S. Food and Drug Administration. FDA issues emergency use authorization for third COVID-19 vaccine. Accessed February 27th, 2022 from. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-third-covid-19-vaccine
50. CDCThe Janssen COVID-19 Vaccine's Local Reactions, Systemic Reactions, Adverse Events, and Serious Adverse Events. Accessed February 27th, 2022 from. https://www.cdc.gov/vaccines/covid-19/info-by-product/janssen/reactogenicity.html
51. See I, Su JR, Lale A, Woo EJ, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448–2456. https://doi.org/10.1001/jama.2021.7517
52. Shay DK, Gee J, Su JR, Myers TR, et al. Safety monitoring of the Janssen (Johnson & Johnson) COVID-19 vaccine - United States, March-April 2021. MMWR Morb Mortal Wkly Rep. 2021;70(18):680–684. https://doi.org/10.15585/mmwr.mm7018e2.
53. Fischer S, Cabrera-Fuentes HA, Noll T, Preissner KT. Impact of extracellular RNA on endothelial barrier function. Cell Tissue Res. 2014;355(3):635–45. https://doi.org/10.1007/s00441-014-1850-8.
54. Nakazawa F, Kannemeier C, Shibamiya A, Song Y, et al. Extracellular RNA is a natural cofactor for the (auto-)activation of Factor VII-activating protease (FSAP). Biochem J. 2005;385(Pt 3):831–8. https://doi.org/10.1042/BJ20041021.
55. Kannemeier C, Shibamiya A, Nakazawa F, Trusheim H, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. Proc Natl Acad Sci U S A. 2007;104(15):6388–93. https://doi.org/10.1073/pnas.0608647104.
56. Fischer S, Gerriets T, Wessels C, Walberer M, et al. Extracellular RNA mediates endothelial-cell permeability via vascular endothelial growth factor. Blood. 2007;110(7):2457–65. https://doi.org/10.1182/blood-2006-08-040691.
57. Verbeke R, Lentacker I, De Smedt SC, Dewitte H. The dawn of mRNA vaccines: the COVID-19 case. J Control Release. 2021;10(333):511–20. https://doi.org/10.1016/j.jconrel.2021.03.043.
58. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261–79. https://doi.org/10.1038/nrd.2017.243.
59. Let's talk about lipid nanoparticles. Nat Rev Mater. 2021;6:99. https://doi.org/10.1038/s41578-021-00281-4.
60. U.S. Food and Drug Administration. FDA takes key action in fight against COVID-19 by issuing emergency use authorization for first COVID-19 vaccine. 2020. Available from. https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19. Accessed 27 Feb 2022
61. Coronavirus (COVID-19) update: FDA authorizes Pfizer-BioNTech COVID-19 vaccine for emergency use in adolescents in another important action in fight against pandemic. https://www.fda.gov/news-events/press-announcements/coron

avirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use. Accessed 27 Feb 2022
62. U.S. Food and Drug Administration. FDA authorizes Pfizer-BioNTech COVID-19 vaccine for emergency use in children 5 through 11 years of age. https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age. Accessed 27 Feb 2022
63. Pfizer-BioNTech COVID-19 Vaccine Reactions & Adverse Events. 2021. Available from. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/reactogenicity.html. Accessed 23 Mar 2022
64. U.S. Food and Drug Administration. FDA takes additional action in fight against COVID-19 by issuing emergency use authorization for second COVID-19 vaccine. Accessed February 27th, 2022.from https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19
65. The Moderna COVID-19 vaccine's local reactions, systemic reactions, adverse events, and serious adverse events. Accessed March 23rd, 2022 from. https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html.
66. Mevorach D, Anis E, Cedar N, Bromberg M, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N Engl J Med. 2021;385(23):2140–9. https://doi.org/10.1056/NEJMoa2109730.
67. Levin D, Shimon G, Fadlon-Derai M, Gershovitz L, et al. Myocarditis following COVID-19 vaccination - a case series. Vaccine. 2021;39(42):6195–200. https://doi.org/10.1016/j.vaccine.2021.09.004.
68. Starekova J, Bluemke DA, Bradham WS, Grist TM, et al. Myocarditis associated with mRNA COVID-19 vaccination. Radiology. 2021;301(2):E409–11. https://doi.org/10.1148/radiol.2021211430.
69. Isaak A, Feisst A, Luetkens JA. Myocarditis following COVID-19 vaccination. Radiology. 2021;301(1):E378–9. https://doi.org/10.1148/radiol.2021211766.
70. Clinical considerations: myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html. Accessed 26 Feb 2022
71. Marshall M, Ferguson ID, Lewis P, Jaggi P, et al. Symptomatic acute myocarditis in 7 adolescents after Pfizer-BioNTech COVID-19 vaccination. Pediatrics. 2021;148(3):e2021052478. https://doi.org/10.1542/peds.2021-052478.
72. Rosner CM, Genovese L, Tehrani BN, Atkins M, et al. Myocarditis temporally associated with COVID-19 vaccination. Circulation. 2021;144(6):502–5. https://doi.org/10.1161/CIRCULATIONAHA.121.055891.
73. Montgomery J, Ryan M, Engler R, Hoffman D, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol. 2021;6(10):1202–6. https://doi.org/10.1001/jamacardio.2021.2833.
74. Oster ME, Shay DK, Su JR, Gee J, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. JAMA. 2022;327(4):331–40. https://doi.org/10.1001/jama.2021.24110.
75. Su JR. Advisory Committee on Immunization Practices January 5, 2022. COVID-19 vaccine safety updates: primary series in children and adolescents ages 5–11 and 12–15 years, and booster doses in adolescents ages 16–24 years. Accessed 26 Feb 2022 from https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/02-covid-su-508.pdf.
76. Dionne A, Sperotto F, Chamberlain S, Baker AL, et al. Association of myocarditis with BNT162b2 messenger RNA COVID-19 vaccine in a case series of children. JAMA Cardiol. 2021;6(12):1446–50. https://doi.org/10.1001/jamacardio.2021.3471.
77. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation. 2021;144(6):471–84. https://doi.org/10.1161/CIRCULATIONAHA.121.056135.
78. CDC COVID-19 Response Team; Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine - United States, December 14–23, 2020. MMWR Morb Mortal Wkly Rep. 2021;70(2):46–51. https://doi.org/10.15585/mmwr.mm7002e1
79. Iguchi T, Umeda H, Kojima M, Kanno Y, et al. Cumulative adverse event reporting of anaphylaxis after mRNA COVID-19 vaccine (Pfizer-BioNTech) injections in Japan: the first-month report. Drug Saf. 2021;44(11):1209–14. https://doi.org/10.1007/s40264-021-01104-9.
80. Blumenthal KG, Robinson LB, Camargo CA Jr, Shenoy ES, Banerji A, et al. Acute allergic reactions to mRNA COVID-19 vaccines. JAMA. 2021;325(15):1562–5. https://doi.org/10.1001/jama.2021.3976.
81. Abi Zeid Daou C, Natout MA, El Hadi N. Biphasic anaphylaxis after exposure to the first dose of Pfizer-BioNTech COVID-19 mRNA vaccine. J Med Virol. 2021;93(10):6027–6029. https://doi.org/10.1002/jmv.27109
82. Shavit R, Maoz-Segal R, Iancovici-Kidon M, Offengenden I, et al. Prevalence of allergic reactions after Pfizer-BioNTech COVID-19 vaccination among adults with high allergy risk. JAMA Netw Open. 2021;4(8):e2122255. https://doi.org/10.1001/jamanetworkopen.2021.22255
83. CDC COVID-19 Response Team; Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine - United States, December 21, 2020-January 10, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(4):125–129. https://doi.org/10.15585/mmwr.mm7004e1
84. Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US-December 14, 2020-January 18, 2021. JAMA. 2021;325(11):1101–2. https://doi.org/10.1001/jama.2021.1967.
85. Mei R, Raschi E, Forcesi E, Diemberger I, et al. Myocarditis and pericarditis after immunization: gaining insights through the Vaccine Adverse Event Reporting System. Int J Cardiol. 2018;15(273):183–6. https://doi.org/10.1016/j.ijcard.2018.09.054.
86. Voleti N, Reddy SP, Ssentongo P. Myocarditis in SARS-CoV-2 infection vs. COVID-19 vaccination: a systematic review and meta-analysis. Front Cardiovasc Med. 2022;9:951314. https://doi.org/10.3389/fcvm.2022.951314
87. Patone M, Mei XW, Handunnetthi L, Dixon S, et al. Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex. Circulation. 2022;146(10):743–54. https://doi.org/10.1161/CIRCULATIONAHA.122.059970.
88. Engler RJ, Nelson MR, Collins LC Jr, Spooner C, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination.PLoS One. 2015;10(3):e0118283. https://doi.org/10.1371/journal.pone.0118283
89. Cassimatis DC, Atwood JE, Engler RM, Linz PE, et al. Smallpox vaccination and myopericarditis: a clinical review. J Am Coll Cardiol. 2004;43(9):1503–10. https://doi.org/10.1016/j.jacc.2003.11.053.
90. Harper NJN, Cook TM, Garcez T, Farmer L, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121(1):159–71. https://doi.org/10.1016/j.bja.2018.04.014.

91. National Center for Immunization and Respiratory Diseases (U.S.).Division of Viral Diseases. Pfizer-BioNTech COVID-19 vaccine (also known as COMIRNATY) overview and safety. https://stacks.cdc.gov/view/cdc/114179. Accessed 22 Mar 2022
92. National Center for Immunization and Respiratory Diseases (U.S.).Division of Viral Diseases, Moderna COVID-19 Vaccine (also known as Spikevax) Overview and Safety. https://stacks.cdc.gov/view/cdc/115700. Accessed 22 Mar 2022
93. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. N Engl J Med. 2021;384(7):643–9. https://doi.org/10.1056/NEJMra2035343.
94. Burn E, Li X, Kostka K, Stewart HM, et al. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries. Pharmacoepidemiol Drug Saf. 2022;31(5):495–510. https://doi.org/10.1002/pds.5419
95. Greinacher A, Thiele T, Warkentin TE, Weisser K, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. 2021;384(22):2092–101. https://doi.org/10.1056/NEJMoa2104840.
96. Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med. 2021;384(20):1964–1965. https://doi.org/10.1056/NEJMc2105869
97. Niesen MJM, Pawlowski C, O'Horo JC, Challener DW, et al. Surveillance of safety of 3 doses of COVID-19 mRNA vaccination using electronic health records.JAMA Netw Open. 1;5(4):e227038. https://doi.org/10.1001/jamanetworkopen.2022.7038
98. Oliver SE, Wallace M, See I, Mbaeyi S, et al. Use of the Janssen (Johnson & Johnson) COVID-19 vaccine: updated interim recommendations from the advisory committee on immunization practices—United States, December 2021. Morb Mortal Wkly Rep. Centers Dis Control Prev. 2022;71:90
99. Mallapaty S. China's COVID vaccines have been crucial - now immunity is waning. Nature. 2021;598(7881):398–9. https://doi.org/10.1038/d41586-021-02796-w.
100. Baraniuk C. What do we know about China's covid-19 vaccines? BMJ. 2021;373:n912. https://doi.org/10.1136/bmj.n912
101. Zhang Y, Zeng G, Pan H, Li C, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181–92. https://doi.org/10.1016/S1473-3099(20)30843-4.
102. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA. 2021;326(1):35–45. https://doi.org/10.1001/jama.2021.8565.
103. Tanriover MD, Doğanay HL, Akova M, Güner HR, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213–22. https://doi.org/10.1016/S0140-6736(21)01429-X.
104. Sinopharm COVID-19 Vaccine (BBIBP-CorV) — Precision Vaccinations. 2021. https://www.precisionvaccinations.com/vaccines/sinopharm-covid-19-vaccine-bbibp-corv. Accessed 14 May 2022
105. Vokó Z, Kiss Z, Surján G, Surján O, et al. Nationwide effectiveness of five SARS-CoV-2 vaccines in Hungary-the HUN-VE study. Clin Microbiol Infect. 2022;28(3):398–404. https://doi.org/10.1016/j.cmi.2021.11.011.
106. Macchia A, Ferrante D, Angeleri P, Biscayart C, et al. Evaluation of a COVID-19 vaccine campaign and SARS-CoV-2 infection and mortality among adults aged 60 years and older in a middle-income country. JAMA Netw Open. 2021;4(10):e2130800. https://doi.org/10.1001/jamanetworkopen.2021.30800
107. Wu S, Huang J, Zhang Z, Wu J, et al. Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: preliminary report of an open-label and randomised phase 1 clinical trial. Lancet Infect Dis. 2021;21(12):1654–64. https://doi.org/10.1016/S1473-3099(21)00396-0.
108. Dai L, Gao L, Tao L, Hadinegoro SR, et al. Efficacy and safety of the RBD-dimer-based Covid-19 vaccine ZF2001 in adults. N Engl J Med. 2022;386(22):2097–111. https://doi.org/10.1056/NEJMoa2202261.
109. Geisbert TW, Bailey M, Hensley L, Asiedu C, et al. Recombinant adenovirus serotype 26 (Ad26) and Ad35 vaccine vectors bypass immunity to Ad5 and protect nonhuman primates against ebolavirus challenge. J Virol. 2011;85(9):4222–33. https://doi.org/10.1128/JVI.02407-10.
110. Larocca RA, Provine NM, Aid M, Iampietro MJ, et al. Adenovirus serotype 5 vaccine vectors trigger IL-27-dependent inhibitory CD4+ T cell responses that impair CD8+ T cell function. Sci Immunol. 2016;1(5):eaaf7643. https://doi.org/10.1126/sciimmunol.aaf7643
111. Stephenson KE, Le Gars M, Sadoff J, de Groot AM, et al. Immunogenicity of the Ad26.COV2.S vaccine for COVID-19. JAMA. 2021;325(15):1535–1544. https://doi.org/10.1001/jama.2021.3645
112. Tukhvatulin AI, Dolzhikova IV, Shcheblyakov DV, Zubkova OV, et al. An open, non-randomised, phase 1/2 trial on the safety, tolerability, and immunogenicity of single-dose vaccine "Sputnik Light" for prevention of coronavirus infection in healthy adults. Lancet Reg Health Eur. 2021;11:100241. https://doi.org/10.1016/j.lanepe.2021.100241
113. Jarynowski A, Semenov A, Kamiński M, Belik V. Mild adverse events of Sputnik V vaccine in Russia: social media content analysis of telegram via deep learning. J Med Internet Res. 2021;23(11):e30529. https://doi.org/10.2196/30529
114. Babamahmoodi F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, et al. Side effects and Immunogenicity following administration of the Sputnik V COVID-19 vaccine in health care workers in Iran. Sci Rep. 2021;11(1):21464. https://doi.org/10.1038/s41598-021-00963-7.
115. Zare H, Rezapour H, Mahmoodzadeh S, Fereidouni M. Prevalence of COVID-19 vaccines (Sputnik V, AZD-1222, and Covaxin) side effects among healthcare workers in Birjand city, Iran. Int Immunopharmacol. 2021;101(Pt B):108351. https://doi.org/10.1016/j.intimp.2021.108351
116. Nogrady B. Mounting evidence suggests Sputnik COVID vaccine is safe and effective. Nature. 2021;595(7867):339–40. https://doi.org/10.1038/d41586-021-01813-2.