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COVID-19 Vaccines Research Literatures

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Abstract: A COVID-19 vaccine is a vaccine intended to provide acquired immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19). Prior to the COVID-19 pandemic, there was an established body of knowledge about the structure and function of coronaviruses causing diseases like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which enabled accelerated development of various vaccine technologies during early 2020. On 10 January 2020, the SARS-CoV-2 genetic sequence data was shared through GISAID, and by 19 March, the global pharmaceutical industry announced a major commitment to address COVID-19. In Phase III trials, several COVID-19 vaccines have demonstrated efficacy as high as 95% in preventing symptomatic COVID-19 infections. As of April 2021, 14 vaccines are authorized by at least one national regulatory authority for public use: two RNA vaccines (Pfizer–BioNTech and Moderna), five conventional inactivated vaccines (BBIBP-CorV, CoronaVac, Covaxin, WIBP-CorV and CoviVac), five viral vector vaccines (Sputnik Light, Sputnik V, Oxford–AstraZeneca, Convidecia, and Johnson & Johnson), and two protein subunit vaccines (EpiVacCorona and RBD-Dimer). In total, as of March 2021, 308 vaccine candidates are in various stages of development, with 73 in clinical research, including 24 in Phase I trials, 33 in Phase I–II trials, and 16 In Phase III development. Many countries have implemented phased distribution plans that prioritize those at highest risk of complications, such as the elderly, and those at high risk of exposure and transmission, such as healthcare workers. Single dose interim use is under consideration in order to extend vaccination to as many people as possible until vaccine availability improves. As of 13 May 2021, 1.4 billion doses of COVID-19 vaccine have been administered worldwide based on official reports from national health agencies. AstraZeneca anticipates producing 3 billion doses in 2021, Pfizer–BioNTech 1.3 billion doses, and Sputnik V, Sinopharm, Sinovac, and Johnson & Johnson 1 billion doses each. Moderna targets producing 600 million doses and Convidecia 500 million doses in 2021. By December 2020, more than ten billion vaccine doses had been preordered by countries, with about half of the doses purchased by high-income countries comprising 14% of the world's population. This article introduces recent research reports as references in the related studies.
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Key words: COVID-19; Vaccines; cell; life; research; literature

Introduction

A COVID-19 vaccine is a vaccine intended to provide acquired immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19). Prior to the COVID-19 pandemic, there was an established body of knowledge about the structure and function of coronaviruses causing diseases like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which enabled accelerated development of various vaccine technologies during early 2020. On 10 January 2020, the SARS-CoV-2 genetic sequence data was shared through GISAID, and by 19 March, the global pharmaceutical industry announced a major commitment to address COVID-19. In Phase III trials, several COVID-19 vaccines have demonstrated efficacy as high as 95% in preventing symptomatic COVID-19 infections. As of April 2021, 14 vaccines are authorized by at least one national regulatory authority for public use: two RNA vaccines (Pfizer–BioNTech and Moderna), five conventional inactivated vaccines (BBIBP-CorV, CoronaVac, Covaxin, WIBP-CorV and CoviVac), five viral vector vaccines (Sputnik Light, Sputnik V, Oxford–AstraZeneca, Convidecia, and Johnson & Johnson), and two protein subunit vaccines (EpiVacCorona and RBD-Dimer). In total, as of March 2021, 308 vaccine candidates are in various stages of development, with 73 in clinical research, including 24 in Phase I trials, 33 in Phase I–II trials, and 16 In Phase III development. Many countries have implemented phased distribution plans that prioritize those at highest risk of complications, such as the elderly, and those at high risk of exposure and

transmission, such as healthcare workers. Single dose interim use is under consideration in order to extend vaccination to as many people as possible until vaccine availability improves. As of 13 May 2021, 1.4 billion doses of COVID-19 vaccine have been administered worldwide based on official reports from national health agencies. AstraZeneca anticipates producing 3 billion doses in 2021, Pfizer–BioNTech 1.3 billion doses, and Sputnik V, Sinopharm, Sinovac, and Johnson & Johnson 1 billion doses each. Moderna targets producing 600 million doses and Convidecia 500 million doses in 2021. By December 2020, more than ten billion vaccine doses had been preordered by countries, with about half of the doses purchased by high-income countries comprising 14% of the world's population. (https://en.wikipedia.org/wiki/COVID-19_vaccine). This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Abedi, F., et al. (2021). "MicroRNAs and SARS-CoV-2 life cycle, pathogenesis, and mutations: biomarkers or therapeutic agents?" Cell Cycle **20**(2): 143-153.

To date, proposed therapies and antiviral drugs have been failed to cure coronavirus disease 2019 (COVID-19) patients. However, at least two drug companies have applied for emergency use authorization with the United States Food and Drug Administration for their coronavirus vaccine candidates and several other vaccines are in various stages of development to determine safety and efficacy. Recently, some studies have shown the role of different human and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) microRNAs (miRNAs) in the pathophysiology of COVID-19. miRNAs are non-coding single-stranded RNAs, which are involved in several physiological and pathological conditions, such as cell proliferation, differentiation, and metabolism. They act as negative regulators of protein synthesis through binding to the 3' untranslated region (3' UTR) of the complementary target mRNA, leading to mRNA degradation or inhibition. The databases of Google Scholar, Scopus, PubMed, and Web of Science were searched for literature regarding the importance of miRNAs in the SARS-CoV-2 life cycle, pathogenesis, and genomic mutations. Furthermore, promising miRNAs as a biomarker or antiviral agent in COVID-19 therapy are reviewed.

Acharya, R. (2020). "Prospective vaccination of COVID-19 using shRNA-plasmid-LDH nanoconjugate." Med Hypotheses **143**: 110084.

COVID-19 is the pandemic outbreak that is caused by SARS-CoV-2 virus from December, 2019. Human race do not know the curative measure of this devastating disease. In today's era of nanotechnology, it may use its knowledge to develop molecular vaccine to combat this disease. In this article we are intended to propose a hypothesis on the development of a vaccine that is molecular in nature to work against COVID-19. The nanoconjugate may comprise with the inorganic nanoparticle layered double hydroxide intercalated with shRNA-plasmid that have a sequence targeting towards the viral genome or viral mRNA. This nanoconjugate may be used as a nasal spray to deliver the shRNA-plasmid to the target site. The nanoconjugate will have several advantages such as they are biocompatible, they forms as stable knockdown to the target cells and they are stable in the nasal mucosa.

Agha, M., et al. (2021). "Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients." medRxiv.

Studies describing SARS-CoV-2 immune responses following mRNA vaccination in hematology malignancy (HM) patients are virtually non-existent. We measured SARS-CoV-2 IgG production in 67 HM patients who received 2 mRNA vaccine doses. We found that 46% of HM patients did not produce antibodies and were therefore vaccine non-responders. Patients with B-cell CLL were at a particularly high risk, as only 23% had detectable antibodies despite the fact that nearly 70% of these patients were not undergoing cancer therapy. HM patients should be counseled about the ongoing risk of COVID-19 despite vaccination. Routine measurement of post-vaccine antibodies in HM patients should be considered. Novel strategies are needed to prevent COVID-19 in these individuals.

Ahammad, I. and S. S. Lira (2020). "Designing a novel mRNA vaccine against SARS-CoV-2: An immunoinformatics approach." Int J Biol Macromol **162**: 820-837.

SARS-CoV-2 is the deadly virus behind COVID-19, the disease that went on to ravage the world and caused the biggest pandemic 21st century has witnessed so far. On the face of ongoing death and destruction, the urgent need for the discovery of a vaccine against the virus is paramount. This study resorted to the emerging discipline of immunoinformatics in order to design a multi-epitope mRNA vaccine against the spike glycoprotein of SARS-CoV-2. Various immunoinformatics tools were utilized to predict T and B lymphocyte epitopes. The epitopes were channeled through a filtering pipeline comprised of antigenicity, toxicity, allergenicity, and cytokine inducibility evaluation with the goal of selecting epitopes capable of generating both T and B

cell-mediated immune responses. Molecular docking simulation between the epitopes and their corresponding MHC molecules was carried out. 13 epitopes, a highly immunogenic adjuvant, elements for proper sub-cellular trafficking, a secretion booster, and appropriate linkers were combined for constructing the vaccine. The vaccine was found to be antigenic, almost neutral at physiological pH, non-toxic, non-allergenic, capable of generating a robust immune response and had a decent worldwide population coverage. Based on these parameters, this design can be considered a promising choice for a vaccine against SARS-CoV-2.

Alexander, J. L., et al. (2021). "SARS-CoV-2 vaccination for patients with inflammatory bowel disease: a British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement." Lancet Gastroenterol Hepatol **6**(3): 218-224.

SARS-CoV-2 has caused a global health crisis and mass vaccination programmes provide the best opportunity for controlling transmission and protecting populations. Despite the impressive clinical trial results of the BNT162b2 (Pfizer/BioNTech), ChAdOx1 nCoV-19 (Oxford/AstraZeneca), and mRNA-1273 (Moderna) vaccines, important unanswered questions remain, especially in patients with pre-existing conditions. In this position statement endorsed by the British Society of Gastroenterology Inflammatory Bowel Disease (IBD) section and IBD Clinical Research Group, we consider SARS-CoV-2 vaccination strategy in patients with IBD. The risks of SARS-CoV-2 vaccination are anticipated to be very low, and we strongly support SARS-CoV-2 vaccination in patients with IBD. Based on data from previous studies with other vaccines, there are conceptual concerns that protective immune responses to SARS-CoV-2 vaccination may be diminished in some patients with IBD, such as those taking anti-TNF drugs. However, the benefits of vaccination, even in patients treated with anti-TNF drugs, are likely to outweigh these theoretical concerns. Key areas for further research are discussed, including vaccine hesitancy and its effect in the IBD community, the effect of immunosuppression on vaccine efficacy, and the search for predictive biomarkers of vaccine success.

Alvi, M. M., et al. (2020). "Pharmacological and non-pharmacological efforts at prevention, mitigation, and treatment for COVID-19." J Drug Target **28**(7-8): 742-754.

A global outbreak of the SARS-CoV-2 virus has infected millions of people over a short period of time. The communicability and increased mortality from the SARS-CoV-2 infection mandated the WHO to declare COVID-19 a worldwide pandemic. The virus outbreak has spread when there are no approved vaccines, treatments, or prophylactic therapies available. Researchers from all over the world have prioritised development of vaccines and antivirals. Several vaccine projects have seen successes in preclinical, phase I, and phase II clinical trials using recombinant DNA, mRNA, live attenuated virus, S-protein subunits, virus like particles, and viral vectors. Initial findings from antivirals such as remdesivir, favipiravir, danoprevir or lopinavir with ritonavir are presented. Immunomodulatory molecules such as sarilumab, tocilizumab, janus kinase inhibitors, and hyperimmune convalescent plasma have mixed outcomes from initial clinical findings; however, pending randomised controlled trials will assist national health institutions to make treatment recommendations for COVID-19. Where compassionate use of remdesivir has shown some benefits, therapies such as hydroxychloroquine have proven harmful due to their toxicities. This review discusses pharmacological interventions at play and evidence-based successes and limitations of non-pharmacological therapies such as social distancing, personal protective equipment, and ventilator support associated with the prevention and treatment of COVID-19.

Amanpour, S. (2021). "The Rapid Development and Early Success of Covid 19 Vaccines Have Raised Hopes for Accelerating the Cancer Treatment Mechanism." Arch Razi Inst **76**(1): 1-6.

The Covid-19 pandemic has brought about rapid change in medical science. The production of new generation vaccines for this disease has surprised even their most optimistic supporters. Not only have these vaccines proven to be effective, but the importance of this disease and pandemic situation also significantly shortened the long-standing process of validating such products. Vaccination is a type of immunotherapy. Researchers have long been looking at vaccines as a possible treatment for cancer (Geynisman et al., 2014). In the same way that vaccines work against infectious diseases, attempts are being made to develop vaccines to identify specific proteins on cancer cells. This helps the immune system recognize and attack cancer cells. Cancer vaccines may help: I) Prevent the growth of cancer cells (Bialkowski et al., 2016), II) Prevent recurrence of cancer (Stanton and Disis, 2015), III) Destroy cancer cells left over from other treatments. The following types of cancer vaccines are being studied: Antigen Vaccines. These vaccines are made from specific proteins or antigens of cancerous cells. Their purpose is to stimulate the immune system to attack cancer cells (Tagliamonte et al., 2014). Whole-Cell Vaccines. A whole-cell vaccine uses the entire cancer cell, not just a specific molecule (antigen), to generate the vaccine. (Keenan and Jaffee,

2012).Dendritic Cell Vaccines. Dendritic cells help the immune system identify abnormal cells, such as cancerous cells. Dendritic cells are grown with cancer cells in the laboratory to produce the vaccine. The vaccine then stimulates the immune system to attack cancer. (Wang et al., 2014; Mastelic-Gavillet et al., 2019). DNA Vaccines. These vaccines are made from DNA fragments of cancer cells. They can be injected into the body to facilitate immune system cells can better respond and kill cancer cells (Gatti-Mays et al., 2017).Other Types of Cancer Vaccines. such as Anti idiotype vaccines. This vaccine stimulates the body to generate antibodies against cancerous cells. An example of an anti-idiotype antibody is Racotumomab or Vaxira (Cancer, 2016). However, conditions and considerations after Corona does not seem to be the same as before. The current pandemic situation has also led to major changes in the pharmaceutical and Vaccine production process and international protocols. Some of the most critical issues that can accelerate the introduction of cancer vaccines are: 1. Typical drug and vaccine development timeline. A typical vaccine needs 5 to 10 years and sometimes longer to design secure funding, and get approval (Figure 1). Less than 10 percent of new drugs, which are entered in the different phases of clinical trials, are advanced to approval by the Food and Drug Administration (FDA)(Cancer, 2020a). However, now the situation is not normal. Dozens of Covid 19 vaccines are starting clinical trials. Some of them use RNA and DNA technology, which delivers the body with missions to produce its antibodies against the virus. There are already at least 254 therapies and 95 vaccines related to Covid-19 being explored. However, it seems that the experiences gained in this pandemic, and advances in technology, may be effective in shortening the production path of other vaccines and drugs and the process of its approval at the national and international levels in the future. In Figure 2, the time course of production of conventional vaccines in comparison with Covid 19 vaccines (Cancer, 2020b) is shown.2. The introduction of messenger RNA (mRNA) technology into the field of prevention and treatment. Over the past decades, this technology has been considered an excellent alternative to conventional vaccination methods. Proper potency and low side effects, the possibility of fast production and relatively low production cost are its advantages. However, until recently, the instability of this molecule has been a major problem in its application. This research was started many years ago by two companies that played a significant role in developing the first Covid vaccines, so BioNTech and Moderna were able to quickly transfer their experience in the field of Covid vaccine development (Pardi et al., 2018; Moderna, 2020). Figure 3 shows how mRNA vaccines work. Bout Pfizer – BioNTech and Moderna mRNA vaccines were more than 90 % effective in preclinical stages. Millions of doses of these two vaccines are currently being injected into eligible individuals worldwide. 3. Considering the use of artificial intelligence in assessing the effectiveness of vaccines. There are always doubts about the effectiveness of the new drug in treating the disease. Once the vaccine is widely available, we will know more about its effectiveness versus it works under carefully controlled scientific testing conditions. Vaccines will continue to be monitored after use. The data collected helps professionals understand how they work in different groups of people (depending on factors such as age, ethnicity, and people with different health conditions) and also the length of protection provided by the vaccine. Artificial intelligence (AI) is an emerging field, which reaches everywhere and not only as a beneficial industrial tool but also as a practical tool in medical science and plays a crucial role in developing the computation vision, risk assessment, diagnostic, prognostic, etc. models in the field of medicine (Amisha et al., 2019). According to the wide range of AI applications in the analysis of different types of data, it can be used in vaccine production, safety assessments, clinical and preclinical studies and Covid 19 vaccines adverse reactions (CDC, 2019). Indeed, most cancer vaccines are therapeutic, rather than prophylactic, and seek to stimulate cell-mediated responses, such as those from CTLs, capable of clearing or reducing tumor burden. There are currently FDA-approved products for helping cancer treatment such as BREYANZI, TECARTUS and YESCARTA for lymphoma, IMLYGIC for melanoma, KYMRIAH for acute lymphoblastic leukemia, and PROVENGE for prostate cancer. Over the past decade, most of BioNTech's activities have been in the field of cancer vaccine design and production for melanoma (two clinical trials), breast cancer (one clinical trial), and the rest concerning viral and veterinary vaccines (two clinical trials). Also Maderno company has been working on Individualized cancer vaccines (one clinical trials), and vaccines for viral infections such as Zika and Influenza and veterinary vaccines (several clinical trials) (Pardi et al., 2018). Therefore, it can be said, mRNA technology that has been the subject of much research into the treatment of cancer has been shifted and rapidly used to produce and use the Covid 19 vaccine. The current pandemic situation has necessitated the acceleration of Covid 19 vaccines and drugs and national and international protocols for their approval. If the currently produced vaccines can continue to be as successful as the preclinical and early phase studies, these changes and evolution have raised hopes for accelerating the use of these technologies and mechanisms in the field of cancer and other diseases vaccines, including HIV and

influenza.

Ayad, C., et al. (2021). "LipoParticles: Lipid-Coated PLA Nanoparticles Enhanced In Vitro mRNA Transfection Compared to Liposomes." Pharmaceutics **13**(3).

The approval of two mRNA vaccines as urgent prophylactic treatments against Covid-19 made them a realistic alternative to conventional vaccination methods. However, naked mRNA is rapidly degraded by the body and cannot effectively penetrate cells. Vectors capable of addressing these issues while allowing endosomal escape are therefore needed. To date, the most widely used vectors for this purpose have been lipid-based vectors. Thus, we have designed an innovative vector called LipoParticles (LP) consisting of poly(lactic) acid (PLA) nanoparticles coated with a 15/85 mol/mol DSPC/DOTAP lipid membrane. An in vitro investigation was carried out to examine whether the incorporation of a solid core offered added value compared to liposomes alone. To that end, a formulation strategy that we have named particulate layer-by-layer (pLbL) was used. This method permitted the adsorption of nucleic acids on the surface of LP (mainly by means of electrostatic interactions through the addition of LAH4-L1 peptide), allowing both cellular penetration and endosomal escape. After a thorough characterization of size, size distribution, and surface charge- and a complexation assessment of each vector-their transfection capacity and cytotoxicity (on antigenic presenting cells, namely DC2.4, and epithelial HeLa cells) were compared. LP have been shown to be significantly better transfecting agents than liposomes through pLbL formulation on both HeLa and DC 2.4 cells. These data illustrate the added value of a solid particulate core inside a lipid membrane, which is expected to rigidify the final assemblies and makes them less prone to early loss of mRNA. In addition, this assembly promoted not only efficient delivery of mRNA, but also of plasmid DNA, making it a versatile nucleic acid carrier that could be used for various vaccine applications. Finally, if the addition of the LAH4-L1 peptide systematically leads to toxicity of the pLbL formulation on DC 2.4 cells, the optimization of the nucleic acid/LAH4-L1 peptide mass ratio becomes an interesting strategy-essentially reducing the peptide intake to limit its cytotoxicity while maintaining a relevant transfection efficiency.

Bartley, J. M., et al. (2021). "Better, Faster, Stronger: mRNA Vaccines Show Promise for Influenza Vaccination in Older Adults." Immunol Invest: 1-11.

Older adults have diminished immune responses that lead to increased susceptibility and severity of infectious diseases. Influenza is a leading killer of older adults despite the availability of seasonal influenza vaccination. Influenza vaccines are strain specific, and their efficacy varies greatly year to year based on how well the vaccine virus matches the circulating strains. Additionally, older adults have reduced vaccination responses. The COVID-19 pandemic highlighted the increased mortality rate in older adults for infectious disease, and brought vaccine development to the forefront. The speed of vaccine development was met with an equally impressive vaccine efficacy. Interestingly, both mRNA-based COVID-19 vaccines currently available have shown similar efficacy in both young and older adults. mRNA vaccine production has significantly reduced the production timeline compared to current influenza vaccines, making them particularly attractive for influenza vaccine development. Faster production coupled with improved efficacy would be a tremendous advancement in protecting older adults from influenza morbidity and mortality.

Batty, C. J., et al. (2021). "Vaccine formulations in clinical development for the prevention of severe acute respiratory syndrome coronavirus 2 infection." Adv Drug Deliv Rev **169**: 168-189.

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an unprecedented effort toward the development of an effective and safe vaccine. Aided by extensive research efforts into characterizing and developing countermeasures towards prior coronavirus epidemics, as well as recent developments of diverse vaccine platform technologies, hundreds of vaccine candidates using dozens of delivery vehicles and routes have been proposed and evaluated preclinically. A high demand coupled with massive effort from researchers has led to the advancement of at least 31 candidate vaccines in clinical trials, many using platforms that have never before been approved for use in humans. This review will address the approach and requirements for a successful vaccine against SARS-CoV-2, the background of the myriad of vaccine platforms currently in clinical trials for COVID-19 prevention, and a summary of the present results of those trials. It concludes with a perspective on formulation problems which remain to be addressed in COVID-19 vaccine development and antigens or adjuvants which may be worth further investigation.

Bisgin, A., et al. (2021). "Current Update on Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Development with a Special Emphasis on Gene Therapy Viral Vector Design and Construction for Vaccination." Hum Gene Ther.

Severe acute respiratory syndrome (SARS) is a newly emerging infectious disease (COVID-19) caused by the novel coronavirus SARS-coronavirus 2

(CoV-2). To combat the devastating spread of SARS-CoV-2, extraordinary efforts from numerous laboratories have focused on the development of effective and safe vaccines. Traditional live-attenuated or inactivated viral vaccines are not recommended for immunocompromised patients as the attenuated virus can still cause disease via phenotypic or genotypic reversion. Subunit vaccines require repeated dosing and adjuvant use to be effective, and DNA vaccines exhibit lower immune responses. mRNA vaccines can be highly unstable under physiological conditions. On the contrary, naturally antigenic viral vectors with well-characterized structure and safety profile serve as among the most effective gene carriers to provoke immune response via heterologous gene transfer. Viral vector-based vaccines induce both an effective cellular immune response and a humoral immune response owing to their natural adjuvant properties via transduction of immune cells. Consequently, viral vectored vaccines carrying the SARS-CoV-2 spike protein have recently been generated and successfully used to activate cytotoxic T cells and develop a neutralizing antibody response. Recent progress in SARS-CoV-2 vaccines, with an emphasis on gene therapy viral vector-based vaccine development, is discussed in this review.

Bleier, B. S., et al. (2021). "COVID-19 Vaccines May Not Prevent Nasal SARS-CoV-2 Infection and Asymptomatic Transmission." Otolaryngol Head Neck Surg **164**(2): 305-307.

Current COVID-19 vaccine candidates are administered by injection and designed to produce an IgG response, preventing viremia and the COVID-19 syndrome. However, systemic respiratory vaccines generally provide limited protection against viral replication and shedding within the airway, as this requires a local mucosal secretory IgA response. Indeed, preclinical studies of adenovirus and mRNA candidate vaccines demonstrated persistent virus in nasal swabs despite preventing COVID-19. This suggests that systemically vaccinated patients, while asymptomatic, may still be become infected and transmit live virus from the upper airway. COVID-19 is known to spread through respiratory droplets and aerosols. Furthermore, significant evidence has shown that many clinic and surgical endonasal procedures are aerosol generating. Until further knowledge is acquired regarding mucosal immunity following systemic vaccination, otolaryngology providers should maintain precautions against viral transmission to protect the proportion of persistently vulnerable patients who exhibit subtotal vaccine efficacy or waning immunity or who defer vaccination.

Bloom, K., et al. (2021). "Self-amplifying RNA vaccines for infectious diseases." Gene Ther **28**(3-4): 117-129.

Vaccinology is shifting toward synthetic RNA platforms which allow for rapid, scalable, and cell-free manufacturing of prophylactic and therapeutic vaccines. The simple development pipeline is based on in vitro transcription of antigen-encoding sequences or immunotherapies as synthetic RNA transcripts, which are then formulated for delivery. This approach may enable a quicker response to emerging disease outbreaks, as is evident from the swift pursuit of RNA vaccine candidates for the global SARS-CoV-2 pandemic. Both conventional and self-amplifying RNAs have shown protective immunization in preclinical studies against multiple infectious diseases including influenza, RSV, Rabies, Ebola, and HIV-1. Self-amplifying RNAs have shown enhanced antigen expression at lower doses compared to conventional mRNA, suggesting this technology may improve immunization. This review will explore how self-amplifying RNAs are emerging as important vaccine candidates for infectious diseases, the advantages of synthetic manufacturing approaches, and their potential for preventing and treating chronic infections.

Brussow, H. (2021). "COVID-19: Vaccination problems." Environ Microbiol.

This minireview addresses problems of financing the vaccine development, regulatory questions, the ethics and efficacy of vaccine prioritization strategies, and the coverage of variant viruses by current vaccines. Serious adverse effects observed with adenovirus vectored vaccines and mRNA vaccines in mass vaccination campaigns are reported. The ethical problems of continuing with placebo controlled vaccine trials and alternative clinical trial protocols are discussed as well as concrete vaccination issues such as the splitting of doses, the delaying of the second dose, the immunization with two different vaccine types, and the need of vaccinating seropositive subjects. Strategies to increase vaccine acceptance in the population are shortly mentioned. This article is protected by copyright. All rights reserved.

Cabanillas, B. and N. Novak (2021). "Allergy to COVID-19 vaccines: A current update." Allergol Int.

Adverse allergic reactions due to the administration of the vaccines developed for the protection of coronavirus disease 2019 (COVID-19) have been reported since the initiation of the vaccination campaigns. Current analyses provided by the Center for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) in the United States have estimated the rates of anaphylactic reactions in 2.5 and 11.1 per million of mRNA-1273

and BNT162b2 vaccines administered, respectively. Although rather low, such rates could have importance due to the uncommon fact that a large majority of the world population will be subjected to vaccination with the aforementioned vaccines in the following months and vaccination will most likely be necessary every season as for influenza vaccines. Health regulators have advised that any subject with a previous history of allergy to drugs or any component of the vaccines should not be vaccinated, however, certain misunderstanding exists since allergy to specific excipients in drugs and vaccines are in occasions misdiagnosed due to an absence of suspicion to specific excipients as allergenic triggers or due to inaccurate labeling or nomenclature. In this review, we provide an updated revision of the most current data regarding the anaphylactic reactions described for BNT162b2 vaccine, mRNA-1273 vaccine, and AZD1222 vaccine. We extensively describe the different excipients in the vaccines with the potential to elicit systemic allergic reactions such as polyethylene glycol (PEG), polysorbates, tromethamine/trometamol, and others and the possible immunological mechanisms involved.

Cabral, B. P., et al. (2021). "Expert Opinions on the Most Promising Treatments and Vaccine Candidates for COVID-19: Global Cross-sectional Survey of Virus Researchers in the Early Months of the Pandemic." JMIR Public Health Surveill **7**(2): e22483.

BACKGROUND: The COVID-19 pandemic presents a great public health challenge worldwide, especially given the urgent need to identify effective drugs and develop a vaccine in a short period of time. Globally, several drugs and vaccine candidates are in clinical trials. However, because these drugs and vaccines are still being tested, there is still no definition of which ones will succeed. OBJECTIVE: This study aimed to assess the opinions of over 1000 virus researchers with knowledge on the prevention and treatment of coronavirus-related human diseases to determine the most promising drug and vaccine candidates to address COVID-19. METHODS: We mapped the clinical trials related to COVID-19 registered at ClinicalTrials.gov. These data were used to prepare a survey questionnaire about treatments and vaccine candidates for COVID-19. In May 2020, a global survey was conducted with authors of recent scientific publications indexed in the Web of Science Core Collection related to viruses, severe acute respiratory syndrome coronavirus, coronaviruses, and COVID-19. RESULTS: Remdesivir, immunoglobulin from cured patients, and plasma were considered to be the most promising treatments in May 2020, while ChAdOx1 and mRNA-1273 were considered to be the most promising vaccine candidates. Almost two-thirds of the respondents (766/1219, 62.8%) believed that vaccines for COVID-19 were likely to be available in the next 18 months. Slightly fewer than 25% (289/1219, 23.7%) believed that a vaccine was feasible, but probably not within 18 months. CONCLUSIONS: The issues addressed in this study are constantly evolving; therefore, the current state of knowledge has changed since the survey was conducted. However, for several months after the survey, the respondents' expectations were in line with recent results related to treatments and vaccine candidates for COVID-19.

Callegaro, A., et al. (2021). "Antibody response to SARS-CoV-2 vaccination is extremely vivacious in subjects with previous SARS-CoV-2 infection." J Med Virol.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic calls for rapid actions, now principally oriented to a world-wide vaccination campaign. In this study we verified if, in individuals with a previous SARS-CoV-2 infection, a single dose of messenger RNA (mRNA) vaccine would be immunologically equivalent to a full vaccine schedule in naive individuals. Health care workers (184) with a previous SARS-CoV-2 infection were sampled soon before the second dose of vaccine and between 7 and 10 days after the second dose, the last sampling time was applied to SARS-CoV-2 naive individuals, too. Antibodies against SARS-CoV-2 were measured using Elecsys Anti-SARS-CoV-2 S immunoassay. The study was powered for non-inferiority. We used non parametric tests and Pearson correlation test to perform inferential analysis. After a single vaccine injection, the median titer of specific antibodies in individuals with previous coronavirus disease 2019 was 30.527 U/ml (interquartile range [IQR]: 19.992-39.288) and in subjects with previous SARS-CoV-2 asymptomatic infection was 19.367.5 U/ml (IQR: 14.688-31.353) ($p = .032$). Both results were far above the median titer in naive individuals after a full vaccination schedule: 1974.5 U/ml (IQR: 895-3455) ($p < .0001$). Adverse events after vaccine injection were more frequent after the second dose of vaccine (mean: 0.95; 95% confidence interval [CI]: 0.75-1.14 vs. mean: 1.91; 95% CI: 1.63-2.19) ($p < .0001$) and in exposed compared to naive (mean: 1.63; 95% CI: 1.28-1.98 vs. mean: 2.35; 95% CI: 1.87-2.82) ($p = .015$). In SARS-CoV-2 naturally infected individuals a single mRNA vaccine dose seems sufficient to reach immunity. Modifying current dosing schedules would speed-up vaccination campaigns.

Calzetta, L., et al. (2021). "Factors Influencing the Efficacy of COVID-19 Vaccines: A Quantitative Synthesis of Phase III Trials." Vaccines (Basel) **9**(4).

To date, there is still a paucity of data from Phase III trials concerning the efficacy of vaccines

against COVID-19. Furthermore, no studies investigated the variables that may modulate the efficacy of vaccination. The aim of this analysis was to assess whether there are modifying factors that may potentially influence the clinical efficacy of COVID-19 vaccines. A quantitative synthesis of data from Phase III trials was performed via pairwise and network meta-analyses, along with meta-regression analysis. Data from Phase III trials are currently available only for AZD1222, BNT162b2, mRNA-1237, and Sputnik V. Vaccination resulted to be generally effective (90.0%, 95%CI 72.6-96.4; $p < 0.001$), although the efficacy of AZD1222 (62.1%) introduced a significant level of heterogeneity in the meta-analysis (I(2) 92.17%, $p < 0.001$). No significant modifying factors resulted from the meta-regression analysis. However, considering the mRNA-based vaccines, a trend toward significance ($p = 0.081$) resulted for age. The network meta-analysis provided the following rank of effectiveness: BNT162b2 approximately mRNA-1273 > Sputnik V >> AZD1222. In conclusion, no modifying factors seem to modulate the efficacy of vaccines against COVID-19. This quantitative synthesis will need to be updated as soon as further clinical results on the efficacy profile are available from Phase III trials for further licensed COVID-19 vaccines.

Checcucci, E., et al. (2020). "The vaccine journey for COVID-19: a comprehensive systematic review of current clinical trials in humans." Panminerva Med.

INTRODUCTION: Since December 2019, there has been an outbreak of a novel beta-coronavirus (SARS-CoV-2) in Wuhan, China. On March the 11th the World Health Organization (WHO) declared COVID-19 as a pandemic, with over 118,000 cases in more than 110 countries around the world. In response to the global coronavirus disease 2019 (COVID-19) emergency, clinical trial research assessing the efficacy and safety of experimental vaccines to prevent COVID-19 are emerging at an unprecedented rate. The aim of this systematic review is to summarize the preliminary experiences and ongoing clinical trials of the major candidates and challenges of the vaccine strategies in humans. EVIDENCE ACQUISITION: After a priori protocol registration with PROSPERO (181483), a systematic research of the published literature was conducted on 24 April 2020 using Medline (via PubMed), Embase (via Ovid), and WHO databases. Moreover, to explore the more recent literature we also searched the preprint server medRxiv. Finally, we scrutinized the Cochrane COVID-19 study register and the COVID-19 section of ClinicalTrials.gov database for identifying relevant ongoing clinical trials. Thereafter we selected the articles according to the PRISMA guidelines. Animal or in-vitro experimental studies were excluded. Moreover editorials, commentaries, abstracts, reviews, book chapters, and articles not in English were not included. EVIDENCE SYNTHESIS: Our search identified 1359 published papers, 478 pre-print articles and 367 ongoing clinical trials. Finally, only ten ongoing clinical trials met the inclusion criteria. Specifically, seven developed vaccines for the S protein of SARS-CoV-2 and three clinical trials assessed the protective role of BCG vaccine against COVID-19. The first group included phase I/II trials with different types of molecules (DNA or mRNA vaccine, bacterial plasmid or viral vectors), the latter were phase III/IV trials designed on the basis of a heterologous lymphocyte activation by the BCG vaccine. CONCLUSIONS: This new disease is pushing the scientific community to develop swiftly a safe and effective vaccine. Notwithstanding the limitations of our analysis, given by the absence of available results, we try to provide a comprehensive view of the ongoing clinical trials in humans. Our analysis reveals a worldwide effort of both scientists and enterprises to achieve one of the most challenging goals of our century.

Chen, R. E., et al. (2021). "Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies." Nat Med **27**(4): 717-726.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the global COVID-19 pandemic. Rapidly spreading SARS-CoV-2 variants may jeopardize newly introduced antibody and vaccine countermeasures. Here, using monoclonal antibodies (mAbs), animal immune sera, human convalescent sera and human sera from recipients of the BNT162b2 mRNA vaccine, we report the impact on antibody neutralization of a panel of authentic SARS-CoV-2 variants including a B.1.1.7 isolate, chimeric strains with South African or Brazilian spike genes and isogenic recombinant viral variants. Many highly neutralizing mAbs engaging the receptor-binding domain or N-terminal domain and most convalescent sera and mRNA vaccine-induced immune sera showed reduced inhibitory activity against viruses containing an E484K spike mutation. As antibodies binding to spike receptor-binding domain and N-terminal domain demonstrate diminished neutralization potency in vitro against some emerging variants, updated mAb cocktails targeting highly conserved regions, enhancement of mAb potency or adjustments to the spike sequences of vaccines may be needed to prevent loss of protection in vivo.

Chervenak, F. A., et al. (2021). "Professionally responsible coronavirus disease 2019 vaccination counseling of obstetrical and gynecologic patients."

Am J Obstet Gynecol **224**(5): 470-478.

The development of coronavirus disease 2019 vaccines in the current and planned clinical trials is essential for the success of a public health response. This paper focuses on how physicians should implement the results of these clinical trials when counseling patients who are pregnant, planning to become pregnant, breastfeeding or planning to breastfeed about vaccines with government authorization for clinical use. Determining the most effective approach to counsel patients about coronavirus disease 2019 vaccination is challenging. We address the professionally responsible counseling of 3 groups of patients-those who are pregnant, those planning to become pregnant, and those breastfeeding or planning to breastfeed. We begin with an evidence-based account of the following 5 major challenges: the limited evidence base, the documented increased risk for severe disease among pregnant coronavirus disease 2019-infected patients, conflicting guidance from government agencies and professional associations, false information about coronavirus disease 2019 vaccines, and maternal mistrust and vaccine hesitancy. We subsequently provide evidence-based, ethically justified, practical guidance for meeting these challenges in the professionally responsible counseling of patients about coronavirus disease 2019 vaccination. To guide the professionally responsible counseling of patients who are pregnant, planning to become pregnant, and breastfeeding or planning to breastfeed, we explain how obstetrician-gynecologists should evaluate the current clinical information, why a recommendation of coronavirus disease 2019 vaccination should be made, and how this assessment should be presented to patients during the informed consent process with the goal of empowering them to make informed decisions. We also present a proactive account of how to respond when patients refuse the recommended vaccination, including the elements of the legal obligation of informed refusal and the ethical obligation to ask patients to reconsider. During this process, the physician should be alert to vaccine hesitancy, ask patients to express their hesitation and reasons for it, and respectfully address them. In contrast to the conflicting guidance from government agencies and professional associations, evidence-based professional ethics in obstetrics and gynecology provides unequivocal and clear guidance: Physicians should recommend coronavirus disease 2019 vaccination to patients who are pregnant, planning to become pregnant, and breastfeeding or planning to breastfeed. To prevent widening of the health inequities, build trust in the health benefits of vaccination, and encourage coronavirus disease 2019 vaccine and treatment uptake, in addition to recommending coronavirus disease 2019 vaccinations, physicians should engage with communities to tailor strategies to overcome mistrust and deliver evidence-based information, robust educational campaigns, and novel approaches to immunization.

Chilamakuri, R. and S. Agarwal (2021). "COVID-19: Characteristics and Therapeutics." Cells **10**(2).

Novel coronavirus (COVID-19 or 2019-nCoV or SARS-CoV-2), which suddenly emerged in December 2019 is still haunting the entire human race and has affected not only the healthcare system but also the global socioeconomic balances. COVID-19 was quickly designated as a global pandemic by the World Health Organization as there have been about 98.0 million confirmed cases and about 2.0 million confirmed deaths, as of January 2021. Although, our understanding of COVID-19 has significantly increased since its outbreak, and multiple treatment approaches and pharmacological interventions have been tested or are currently under development to mitigate its risk-factors. Recently, some vaccine candidates showed around 95% clinical efficacy, and now receiving emergency use approvals in different countries. US FDA recently approved BNT162 and mRNA-1273 vaccines developed by Pfizer/BioNTech and Moderna Inc. for emergency use and vaccination in the USA. In this review, we present a succinct overview of the SARS-CoV-2 virus structure, molecular mechanisms of infection, COVID-19 epidemiology, diagnosis, and clinical manifestations. We also systematize different treatment strategies and clinical trials initiated after the pandemic outbreak, based on viral infection and replication mechanisms. Additionally, we reviewed the novel pharmacological intervention approaches and vaccine development strategies against COVID-19. We speculate that the current pandemic emergency will trigger detailed studies of coronaviruses, their mechanism of infection, development of systematic drug repurposing approaches, and novel drug discoveries for current and future pandemic outbreaks.

Chilimuri, S., et al. (2021). "COVID-19 Vaccine Failure in a Patient with Multiple Sclerosis on Ocrelizumab." Vaccines (Basel) **9**(3).

Vaccines will play a key role in ending the COVID-19 pandemic. Vaccination against infections remains an important part of the management of patients with multiple sclerosis. However, there are limited data about the safety and efficacy of the currently available COVID-19 mRNA vaccines in patients with multiple sclerosis receiving concurrent immunosuppressive therapies. Patients on B cell depleting therapy such as ocrelizumab have an attenuated vaccine response. We report the first case of COVID-19 vaccine failure in a patient with relapsing-

remitting multiple sclerosis on B cell depleting therapy, ocrelizumab. We offer suggestions to improve vaccine efficacy in these patients.

Chirumbolo, S. (2021). "Vaccination hesitancy and the "myth" on mRNA-based vaccines in Italy in the COVID-19 era: Does urgency meet major safety criteria?" J Med Virol.

Coronavirus disease 2019 (COVID-19) vaccination campaign in Italy has started with a huge perplexity about vaccine efficacy, vaccine-borne adverse effects and vaccine clinical trial studies. In this commentary I tried to elucidate these issues, which represent a fundamental topic to be thoroughly addressed in COVID-19 pandemic.

Chu, L., et al. (2021). "A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine." Vaccine **39**(20): 2791-2799.

BACKGROUND: Vaccines are urgently needed to prevent the global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We assessed the safety and immunogenicity of vaccine candidate mRNA-1273, encoding the prefusion-stabilized spike protein of SARS-CoV-2. METHODS: This phase 2, randomized, observer-blind, placebo-controlled trial was conducted at 8 sites in the USA, in healthy adults aged >/=18 years with no known history or risk of SARS-CoV-2 infection, and had not previously received an investigational CoV vaccine or treatment. Participants were stratified into two age cohorts (>/=18-<55 and >/=55) and were randomly assigned (1:1:1) to either 50 or 100 microg of mRNA-1273, or placebo administered as two intramuscular injections 28 days apart. The primary outcomes were safety, reactogenicity, and immunogenicity assessed by anti-SARS-CoV-2-spike binding antibody level (bAb). Secondary outcome was immunogenicity assessed by SARS-CoV-2 neutralizing antibody (nAb) response. RESULTS: Between 29 May and 8 July 2020, 600 participants were randomized, 300 per age cohort. The most common solicited adverse reactions were pain at injection site, headache, and fatigue following each vaccination in both age cohorts. One serious adverse event deemed unrelated by the site investigator occurred 33 days post-vaccination one. mRNA-1273 induced bAb and nAb by 28 days post-vaccination one that were higher at the 100 microg dose relative to the 50 microg dose; this difference was less apparent post-vaccination two. Binding antibodies and nAb increased substantially by 14 days following the second vaccination (day 43) to levels exceeding those of convalescent sera and remained elevated through day 57. CONCLUSIONS: Vaccination with mRNA-1273 resulted in significant immune responses to SARS-CoV-2 in participants 18 years and older, with an acceptable safety profile, confirming the safety and immunogenicity of 50 and 100 microg mRNA-1273 given as a 2 dose-regimen. ClinicalTrials.gov; NCT04405076.

Chung, J. Y., et al. (2021). "COVID-19 vaccines: The status and perspectives in delivery points of view." Adv Drug Deliv Rev **170**: 1-25.

Due to the high prevalence and long incubation periods often without symptoms, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected millions of individuals globally, causing the coronavirus disease 2019 (COVID-19) pandemic. Even with the recent approval of the anti-viral drug, remdesivir, and Emergency Use Authorization of monoclonal antibodies against S protein, bamlanivimab and casirimab/imdevimab, efficient and safe COVID-19 vaccines are still desperately demanded not only to prevent its spread but also to restore social and economic activities via generating mass immunization. Recent Emergency Use Authorization of Pfizer and BioNTech's mRNA vaccine may provide a pathway forward, but monitoring of long-term immunity is still required, and diverse candidates are still under development. As the knowledge of SARS-CoV-2 pathogenesis and interactions with the immune system continues to evolve, a variety of drug candidates are under investigation and in clinical trials. Potential vaccines and therapeutics against COVID-19 include repurposed drugs, monoclonal antibodies, antiviral and antigenic proteins, peptides, and genetically engineered viruses. This paper reviews the virology and immunology of SARS-CoV-2, alternative therapies for COVID-19 to vaccination, principles and design considerations in COVID-19 vaccine development, and the promises and roles of vaccine carriers in addressing the unique immunopathological challenges presented by the disease.

Chung, Y. H., et al. (2020). "COVID-19 Vaccine Frontrunners and Their Nanotechnology Design." ACS Nano **14**(10): 12522-12537.

Humanity is experiencing a catastrophic pandemic. SARS-CoV-2 has spread globally to cause significant morbidity and mortality, and there still remain unknowns about the biology and pathology of the virus. Even with testing, tracing, and social distancing, many countries are struggling to contain SARS-CoV-2. COVID-19 will only be suppressible when herd immunity develops, either because of an effective vaccine or if the population has been infected and is resistant to reinfection. There is virtually no chance of a return to pre-COVID-19 societal behavior until there is an effective vaccine. Concerted efforts by physicians, academic laboratories, and companies

around the world have improved detection and treatment and made promising early steps, developing many vaccine candidates at a pace that has been unmatched for prior diseases. As of August 11, 2020, 28 of these companies have advanced into clinical trials with Moderna, CanSino, the University of Oxford, BioNTech, Sinovac, Sinopharm, Anhui Zhifei Longcom, Inovio, Novavax, Vaxine, Zydus Cadila, Institute of Medical Biology, and the Gamaleya Research Institute having moved beyond their initial safety and immunogenicity studies. This review analyzes these frontrunners in the vaccine development space and delves into their posted results while highlighting the role of the nanotechnologies applied by all the vaccine developers.

Cirillo, N. (2021). "Reported orofacial adverse effects of COVID-19 vaccines: The knowns and the unknowns." J Oral Pathol Med **50**(4): 424-427.

INTRODUCTION: Adverse events associated with vaccine administration can manifest in the oral cavity and orofacial region. Hence, the aim of this study was to compare the orofacial adverse effects of two recently authorised COVID-19 vaccines, namely BNT162b2 and mRNA-1273. METHODS: Publicly available data on BNT162b2 and mRNA-1273 vaccines were accessed from the relevant regulatory authorities in the United States, Canada, European Union and United Kingdom. Both patient/recipient information and healthcare professional fact sheets for each of these drugs were manually searched to find their orofacial adverse effects. RESULTS: Adverse events affecting the orofacial region were reported for both vaccines. These were rare and included acute peripheral facial paralysis (Bell's palsy), facial swelling, and swelling of the lips, face or tongue associated with anaphylaxis. There was heterogeneity in the acknowledgement of vaccine-related adverse events in North America compared with Europe. CONCLUSION: Globally, there are inconsistencies in the description of adverse effects presenting in the orofacial region of the COVID-19 vaccines BNT162b2 and mRNA-1273. We believe that awareness of these orofacial manifestations will improve recognition, management and reporting of vaccine-related adverse effects.

Clark, L. K., et al. (2020). "Structure of nonstructural protein 1 from SARS-CoV-2." bioRxiv.

The periodic emergence of novel coronaviruses (CoVs) represents an ongoing public health concern with significant health and financial burden worldwide. The most recent occurrence originated in the city of Wuhan, China where a novel coronavirus (SARS-CoV-2) emerged causing severe respiratory illness and pneumonia. The continual emergence of novel coronaviruses underscores the importance of developing effective vaccines as well as novel therapeutic options that target either viral functions or host factors recruited to support coronavirus replication. The CoV nonstructural protein 1 (nsp1) has been shown to promote cellular mRNA degradation, block host cell translation, and inhibit the innate immune response to virus infection. Interestingly, deletion of the nsp1-coding region in infectious clones prevented the virus from productively infecting cultured cells. Because of nsp1's importance in the CoV lifecycle, it has been highlighted as a viable target for both antiviral therapy and vaccine development. However, the fundamental molecular and structural mechanisms that underlie nsp1 function remain poorly understood, despite its critical role in the viral lifecycle. Here we report the high-resolution crystal structure of the amino, globular portion of SARS-CoV-2 nsp1 (residues 10 - 127) at 1.77A resolution. A comparison of our structure with the SARS-CoV-1 nsp1 structure reveals how mutations alter the conformation of flexible loops, inducing the formation of novel secondary structural elements and new surface features. Paired with the recently published structure of the carboxyl end of nsp1 (residues 148 - 180), our results provide the groundwork for future studies focusing on SARS-CoV-2 nsp1 structure and function during the viral lifecycle. IMPORTANCE: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent for the COVID-19 pandemic. One protein known to play a critical role in the coronavirus lifecycle is nonstructural protein1 (nsp1). As such, it has been highlighted in numerous studies as a target for both the development of antivirals and for the design of live-attenuated vaccines. Here we report the high-resolution crystal structure of nsp1 derived from SARS-CoV-2 at 1.77A resolution. This structure will facilitate future studies focusing on understanding the relationship between structure and function for nsp1. In turn, understanding these structure-function relationships will allow nsp1 to be fully exploited as a target for both antiviral development and vaccine design.

Clark, L. K., et al. (2021). "Structure of Nonstructural Protein 1 from SARS-CoV-2." J Virol **95**(4).

The periodic emergence of novel coronaviruses (CoVs) represents an ongoing public health concern with significant health and financial burdens worldwide. The most recent occurrence originated in the city of Wuhan, China, where a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged causing severe respiratory illness and pneumonia. The continual emergence of novel coronaviruses underscores the importance of developing effective vaccines as well as novel therapeutic options that target either viral

functions or host factors recruited to support coronavirus replication. The CoV nonstructural protein 1 (nsp1) has been shown to promote cellular mRNA degradation, block host cell translation, and inhibit the innate immune response to virus infection. Interestingly, deletion of the nsp1-coding region in infectious clones prevented the virus from productively infecting cultured cells. Because of nsp1's importance in the CoV life cycle, it has been highlighted as a viable target for both antiviral therapy and vaccine development. However, the fundamental molecular and structural mechanisms that underlie nsp1 function remain poorly understood, despite its critical role in the viral life cycle. Here, we report the high-resolution crystal structure of the amino globular portion of SARS-CoV-2 nsp1 (residues 10 to 127) at 1.77-A resolution. A comparison of our structure with the SARS-CoV-1 nsp1 structure reveals how mutations alter the conformation of flexible loops, inducing the formation of novel secondary structural elements and new surface features. Paired with the recently published structure of the carboxyl end of nsp1 (residues 148 to 180), our results provide the groundwork for future studies focusing on SARS-CoV-2 nsp1 structure and function during the viral life cycle.IMPORTANCE Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the COVID-19 pandemic. One protein known to play a critical role in the coronavirus life cycle is nonstructural protein 1 (nsp1). As such, it has been highlighted in numerous studies as a target for both the development of antivirals and the design of live-attenuated vaccines. Here, we report the high-resolution crystal structure of nsp1 derived from SARS-CoV-2 at 1.77-A resolution. This structure will facilitate future studies focusing on understanding the relationship between structure and function for nsp1. In turn, understanding these structure-function relationships will allow nsp1 to be fully exploited as a target for both antiviral development and vaccine design.

Cohen, D., et al. (2021). "Hypermetabolic lymphadenopathy following administration of BNT162b2 mRNA Covid-19 vaccine: incidence assessed by [(18)F]FDG PET-CT and relevance to study interpretation." Eur J Nucl Med Mol Imaging **48**(6): 1854-1863.

PURPOSE: Nationwide mass vaccination against Covid-19 started in Israel in late 2020. Soon we identified on [(18)F]FDG PET-CT studies vaccine-associated hypermetabolic lymphadenopathy (VAHL) in axillary or supraclavicular lymph nodes (ASLN) ipsilateral to the vaccination site. Sometimes, differentiation between the malignant and benign nature of the hypermetabolic lymphadenopathy (HLN) could not be made, and equivocal HLN (EqHL) was reported. The purpose of the study was to determine the overall incidence of VAHL after BNT162b2 vaccination and also its relevance to PET-CT interpretation in oncologic patients. METHODS: A total of 951 consecutive patients that underwent [(18)F]FDG PET-CT studies in our department were interviewed regarding the sites and dates of the vaccine doses. A total of 728 vaccinated patients (All-Vac group) were included: 346 received the first dose only (Vac-1 group) and 382 received the booster dose as well (Vac-2 group). Studies were categorized as no HLN, malignant-HLN (MHL), VAHL, or EqHL. In studies with VAHL, location, [(18)F]FDG-intensity uptake and nodes size were recorded. RESULTS: The incidences of HLN were 45.6%, 36.4%, and 53.9% in All-Vac, Vac-1, and Vac-2 groups, respectively. VAHL was reported in 80.1% of vaccinated patients with HLN. Lower incidences of VAHL were found during the first 5 days or in the third week after the first vaccine and beyond 20 days after the booster dose. In 49 of 332 (14.8%) vaccinated patients, we could not determine whether HLN was MHL or VAHL. Breast cancer and lymphoma were the leading diseases with EqHL. CONCLUSION: VAHL is frequently observed after BNT162b2 administration, more commonly and with higher intensity following the booster dose. To minimize false and equivocal reports in oncological patients, timing of [(18)F]FDG PET-CT should be based on the time intervals found to have a lower incidence of VAHL, and choice of vaccine injection site should be advised, mainly in patients where ASLN are a relevant site of tumor involvement.

Copur, M. (2021). "Messenger RNA Vaccines: Beckoning of a New Era in Cancer Immunotherapy." Oncology (Williston Park) **35**(4): 190-198.

Messenger RNA (mRNA) vaccines are a relatively new class of vaccines. They combine the potential of mRNA to encode for almost any protein with an excellent safety profile and a flexible production process. During the last decade, the mRNA vaccine approach has been increasingly recognized and viewed as a versatile tool for the development of new innovative therapeutics not only in infectious disease settings but also in cancer. mRNA vaccines traditionally consist of a messenger RNA synthesized by in vitro transcription using a bacteriophage RNA polymerase and a template DNA that encodes the antigen(s) of interest. Once administered and internalized by host cells, the mRNA transcripts are translated directly in the cytoplasm of the cell. The resulting antigens are presented to the immune system cells to stimulate an immune response. Dendritic cells (DCs) can be utilized as a carrier by delivering tumor-associated antigen mRNAs or total tumor RNA to their

cytoplasm; then, the mRNA-loaded DCs can be delivered to the host to elicit a specific immune response. Recently, 2 mRNA vaccines were approved for the first time for human use-to prevent COVID-19 infection-bringing excitement for the future possibilities of this approach for cancer immunotherapy as well as for preventing other infectious diseases.

Corbett, K. S., et al. (2020). "SARS-CoV-2 mRNA Vaccine Development Enabled by Prototype Pathogen Preparedness." bioRxiv.

A SARS-CoV-2 vaccine is needed to control the global COVID-19 public health crisis. Atomic-level structures directed the application of prefusion-stabilizing mutations that improved expression and immunogenicity of betacoronavirus spike proteins. Using this established immunogen design, the release of SARS-CoV-2 sequences triggered immediate rapid manufacturing of an mRNA vaccine expressing the prefusion-stabilized SARS-CoV-2 spike trimer (mRNA-1273). Here, we show that mRNA-1273 induces both potent neutralizing antibody and CD8 T cell responses and protects against SARS-CoV-2 infection in lungs and noses of mice without evidence of immunopathology. mRNA-1273 is currently in a Phase 2 clinical trial with a trajectory towards Phase 3 efficacy evaluation.

Corbett, K. S., et al. (2020). "SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness." Nature **586**(7830): 567-571.

A vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is needed to control the coronavirus disease 2019 (COVID-19) global pandemic. Structural studies have led to the development of mutations that stabilize Betacoronavirus spike proteins in the prefusion state, improving their expression and increasing immunogenicity(1). This principle has been applied to design mRNA-1273, an mRNA vaccine that encodes a SARS-CoV-2 spike protein that is stabilized in the prefusion conformation. Here we show that mRNA-1273 induces potent neutralizing antibody responses to both wild-type (D614) and D614G mutant(2) SARS-CoV-2 as well as CD8(+) T cell responses, and protects against SARS-CoV-2 infection in the lungs and noses of mice without evidence of immunopathology. mRNA-1273 is currently in a phase III trial to evaluate its efficacy.

Corbett, K. S., et al. (2020). "Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates." N Engl J Med **383**(16): 1544-1555.

BACKGROUND: Vaccines to prevent coronavirus disease 2019 (Covid-19) are urgently needed. The effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines on viral replication in both upper and lower airways is important to evaluate in nonhuman primates. METHODS: Nonhuman primates received 10 or 100 mug of mRNA-1273, a vaccine encoding the prefusion-stabilized spike protein of SARS-CoV-2, or no vaccine. Antibody and T-cell responses were assessed before upper- and lower-airway challenge with SARS-CoV-2. Active viral replication and viral genomes in bronchoalveolar-lavage (BAL) fluid and nasal swab specimens were assessed by polymerase chain reaction, and histopathological analysis and viral quantification were performed on lung-tissue specimens. RESULTS: The mRNA-1273 vaccine candidate induced antibody levels exceeding those in human convalescent-phase serum, with live-virus reciprocal 50% inhibitory dilution (ID50) geometric mean titers of 501 in the 10-mug dose group and 3481 in the 100-mug dose group. Vaccination induced type 1 helper T-cell (Th1)-biased CD4 T-cell responses and low or undetectable Th2 or CD8 T-cell responses. Viral replication was not detectable in BAL fluid by day 2 after challenge in seven of eight animals in both vaccinated groups. No viral replication was detectable in the nose of any of the eight animals in the 100-mug dose group by day 2 after challenge, and limited inflammation or detectable viral genome or antigen was noted in lungs of animals in either vaccine group. CONCLUSIONS: Vaccination of nonhuman primates with mRNA-1273 induced robust SARS-CoV-2 neutralizing activity, rapid protection in the upper and lower airways, and no pathologic changes in the lung. (Funded by the National Institutes of Health and others.).

Corti, C., et al. (2021). "SARS-CoV-2 vaccines for cancer patients: a call to action." Eur J Cancer **148**: 316-327.

Coronavirus disease 2019 (COVID-19) has affected more than 96 million people worldwide, leading the World Health Organization (WHO) to declare a pandemic in March 2020. Although an optimal medical treatment of COVID-19 remains uncertain, an unprecedented global effort to develop an effective vaccine hopes to restore pre-pandemic conditions. Since cancer patients as a group have been shown to be at a higher risk of severe COVID-19, the development of safe and effective vaccines is crucial. However, cancer patients may be underrepresented in ongoing phase 3 randomised clinical trials investigating COVID-19 vaccines. Therefore, we encourage stakeholders to provide real-time data about the characteristics of recruited participants, including clearly identifiable subgroups, like cancer patients, with sample sizes large enough to determine safety and efficacy. Moreover, we envisage a prompt implementation of suitable registries for

pharmacovigilance reporting, in order to monitor the effects of COVID-19 vaccines and immunisation rates in patients with cancer. That said, data extrapolation from other vaccine trials (e.g. anti-influenza virus) showed a favourable safety and efficacy profile for cancer patients. On the basis of the evidence discussed, we believe that the benefits of the vaccination outweigh the risks. Consequently, healthcare authorities should prioritise vaccinations for cancer patients, with the time-point of administration agreed on a case-by-case basis. In this regard, the American Society of Clinical Oncology and the European Society of Medical Oncology are advocating for cancer patients a high priority status, in the hope of attenuating the consequences of the pandemic in this particularly vulnerable population.

Costa Frossard-Franca, L., et al. (2021). "[Vaccination against SARS-CoV-2 in patients with multiple sclerosis]." Rev Neurol **72**(7): 250-260.

INTRODUCTION: The recent availability of SARS-CoV-2 vaccines has raised concerns in certain patient groups, such as those with multiple sclerosis. However, there are currently few publications that provide information on this issue. We pooled the information available on the safety and efficacy of vaccination against SARS-CoV-2 in patients with multiple sclerosis, with and without disease-modifying therapy. DEVELOPMENT: The study consisted in a literature search focused on the types of SARS-CoV-2 vaccines, the current status of their approval, and the data available on the safety and efficacy of vaccines in patients with multiple sclerosis, including the new COVID-19 vaccines. Based on this search, the document has been designed taking into account current evidence and expert recommendations. There are no data on the safety and efficacy of SARS-CoV-2 vaccines in patients with multiple sclerosis. However, evidence does exist to suggest that messenger RNA (mRNA) vaccines against SARS-CoV-2 are as safe in these patients as in other individuals. Some therapies with immunosuppressants might reduce the effectiveness of these vaccines and require the scheduling of their administration, preferably before the start of treatment if possible. CONCLUSION: The data available make it possible to recommend mRNA vaccines against SARS-CoV-2 in patients with multiple sclerosis. In patients on fingolimod, cladribine, alemtuzumab, ocrelizumab and rituximab, vaccination prior to the initiation of medication administration would be recommendable whenever possible.

Craig, A. M., et al. (2021). "Coronavirus disease 2019 vaccines in pregnancy." Am J Obstet Gynecol MFM **3**(2): 100295.

As of December 1, 2020, nearly 64 million people have been infected with the severe acute respiratory syndrome coronavirus 2 worldwide with nearly 1.5 million global deaths. The impact of this virus has continued to overwhelm hospital infrastructure and demanded remodeling of healthcare systems. With rising concerns for a third, and possibly the largest, wave of individuals infected with the virus, national leaders are continuing to seek avenues by which we can further limit disease transmission and prevent infection with the use of vaccination. To our knowledge, no clinical trial evaluating vaccines to prevent coronavirus disease 2019 has included pregnant women. In December 2020, it was anticipated that the Food and Drug Administration will approve at least 1 or 2 mRNA-based coronavirus disease 2019 vaccine under the Emergency Use Authorization based on phase 3 clinical trial efficacy data. Both Pfizer and Moderna have manufactured mRNA-based vaccines with 95% and 94.1% efficacy against the severe acute respiratory syndrome coronavirus 2. AstraZeneca has manufactured a vaccine using a viral vector demonstrating early efficacy as well, and this next-generation platform has previously been utilized with the Ebola vaccine and safely administered during pregnancy with an acceptable safety profile. Approval of these vaccines will have a tremendous impact on the ongoing pandemic, yet there remains a lack of data for use of coronavirus disease 2019 vaccine in pregnant women. In this article, we seek to discuss the available data regarding treatment and prevention of coronavirus disease 2019 in pregnancy and address the growing questions regarding how best to approach vaccine access and administration in the pregnant population.

de Alwis, R., et al. (2021). "A single dose of self-transcribing and replicating RNA-based SARS-CoV-2 vaccine produces protective adaptive immunity in mice." Mol Ther.

A self-transcribing and replicating RNA (STARR)-based vaccine (LUNAR-COV19) has been developed to prevent SARS-CoV-2 infection. The vaccine encodes an alphavirus-based replicon and the SARS-CoV-2 full-length spike glycoprotein. Translation of the replicon produces a replicase complex that amplifies and prolongs SARS-CoV-2 spike glycoprotein expression. A single prime vaccination in mice led to robust antibody responses, with neutralizing antibody titers increasing up to day 60. Activation of cell-mediated immunity produced a strong viral antigen-specific CD8(+) T lymphocyte response. Assaying for intracellular cytokine staining for interferon (IFN)gamma and interleukin-4 (IL-4)-positive CD4(+) T helper (Th) lymphocytes as well as anti-spike glycoprotein immunoglobulin G (IgG)2a/IgG1 ratios supported a strong Th1-dominant immune response. Finally, single LUNAR-COV19

vaccination at both 2 mug and 10 mug doses completely protected human ACE2 transgenic mice from both mortality and even measurable infection following wild-type SARS-CoV-2 challenge. Our findings collectively suggest the potential of LUNAR-COV19 as a single-dose vaccine.

De Leon-Rodriguez, S. G., et al. (2020). "SARS-CoV-2: previous coronaviruses, immune response, and development of vaccines." Bol Med Hosp Infant Mex **77**(5): 252-261.

Since the emergence of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China at the end of 2019, when its characteristics were practically unknown, one aspect was evident: its high contagion rate. This high infection rate resulted in the spread of the virus in China, Europe, and, eventually, the rest of the world, including Mexico. At present, around 9 million people are infected, and around 470,000 have died worldwide. In this context, the need to generate protective immunity, and especially the generation of a vaccine that can protect the world population against infection in the shortest possible time, is a challenge that is being addressed in different countries using different strategies in multiple clinical trials. This opinion article will present the evidence of the induction of immune response in some of the viruses of the coronavirus family before COVID-19, such as SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus). The information collected about the induction of an immune response by SARS-CoV-2 will be presented, as well as a description of the vaccine candidates reported to date in the various ongoing clinical trials. Finally, an opinion based on the evidence presented will be issued on the potential success of developing vaccine prototypes.

De Salazar, P. M., et al. (2021). "High coverage COVID-19 mRNA vaccination rapidly controls SARS-CoV-2 transmission in Long-Term Care Facilities." medRxiv.

Residents of Long-Term Care Facilities (LTCFs) represent a major share of COVID-19 deaths worldwide. Information on vaccine effectiveness in these settings is essential to improve mitigation strategies, but evidence remains limited. To evaluate the early effect of the administration of BNT162b2 mRNA vaccines in LTCFs, we monitored subsequent SARS-CoV-2 documented infections and deaths in Catalonia, a region of Spain, and compared them to counterfactual model predictions from February 6th to March 28th, 2021, the subsequent time period after which 70% of residents were fully vaccinated. We calculated the reduction in SARS-CoV-2 documented infections and deaths as well as the detected county-level transmission. We estimated that once more than 70% of the LTCFs population were fully vaccinated, 74% (58%-81%, 90% CI) of COVID-19 deaths and 75% (36%-86%) of all documented infections were prevented. Further, detectable transmission was reduced up to 90% (76-93%). Our findings provide evidence that high-coverage vaccination is the most effective intervention to prevent SARS-CoV-2 transmission and death. Widespread vaccination could be a feasible avenue to control the COVID-19 pandemic.

Deepak, P., et al. (2021). "Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2." medRxiv.

Background: Individuals with chronic inflammatory diseases (CID) are frequently treated with immunosuppressive medications that can increase their risk of severe COVID-19. While novel mRNA-based SARS-CoV-2 vaccination platforms provide robust protection in immunocompetent individuals, the immunogenicity in CID patients on immunosuppression is not well established. Therefore, determining the effectiveness of SARS-CoV-2 vaccines in the setting of immunosuppression is essential to risk-stratify CID patients with impaired protection and provide clinical guidance regarding medication management. Methods: We conducted a prospective assessment of mRNA-based vaccine immunogenicity in 133 adults with CIDs and 53 immunocompetent controls. Blood from participants over 18 years of age was collected before initial immunization and 1-2 weeks after the second immunization. Serum anti-SARS-CoV-2 spike (S) IgG (+) binding, neutralizing antibody titers, and circulating S-specific plasmablasts were quantified to assess the magnitude and quality of the humoral response following vaccination. Results: Compared to immunocompetent controls, a three-fold reduction in anti-S IgG titers (P=0.009) and SARS-CoV-2 neutralization (p<0.0001) were observed in CID patients. B cell depletion and glucocorticoids exerted the strongest effect with a 36- and 10-fold reduction in humoral responses, respectively (p<0.0001). Janus kinase inhibitors and antimetabolites, including methotrexate, also blunted antibody titers in multivariate regression analysis (P<0.0001, P=0.0023, respectively). Other targeted therapies, such as TNF inhibitors, IL-12/23 inhibitors, and integrin inhibitors, had only modest impacts on antibody formation and neutralization. Conclusions: CID patients treated with immunosuppressive therapies exhibit impaired SARS-CoV-2 vaccine-induced immunity, with glucocorticoids and B cell depletion therapy more severely impeding optimal responses.

DeGrazia, D. and F. G. Miller (2021). "SARS-CoV-2 Infection Challenge Experiments in Nonhuman

Primates: An Ethical Perspective." Clin Infect Dis.

The COVID-19 pandemic has stimulated massive investment in biomedical research with the aims of understanding the disease and developing effective vaccine and therapeutic interventions. What role should animal research play in this scientific endeavor? Both the urgency to evaluate candidate interventions for human use and growing societal concern about ethical treatment of (nonhuman) animals put into question the justifiability of animal research as a precursor to clinical trials. Yet forgoing animal research in the rush to undertake human testing might expose human research participants to unacceptable risks. In this article, we apply a recently developed framework of principles for animal research ethics in exploring ethical questions raised by a SARS-CoV-2 infection challenge experiment involving rhesus macaques, which evaluated the protective efficacy of the mRNA-1273 vaccine that was recently approved for emergency use. Our aim is to illuminate the ethical issues while introducing, and illustrating the use of, the framework.

Demoulins, T., et al. (2020). "Self-Amplifying Pestivirus Replicon RNA Encoding Influenza Virus Nucleoprotein and Hemagglutinin Promote Humoral and Cellular Immune Responses in Pigs." Front Immunol **11**: 622385.

Self-amplifying replicon RNA (RepRNA) promotes expansion of mRNA templates encoding genes of interest through their replicative nature, thus providing increased antigen payloads. RepRNA derived from the non-cytopathogenic classical swine fever virus (CSFV) targets monocytes and dendritic cells (DCs), potentially promoting prolonged antigen expression in the DCs, contrasting with cytopathogenic RepRNA. We engineered pestivirus RepRNA constructs encoding influenza virus H5N1 (A/chicken/Yamaguchi/7/2004) nucleoprotein (Rep-NP) or hemagglutinin (Rep-HA). The inherent RNase-sensitivity of RepRNA had to be circumvented to ensure efficient delivery to DCs for intracellular release and RepRNA translation; we have reported how only particular synthetic delivery vehicle formulations are appropriate. The question remained concerning RepRNA packaged in virus replicon particles (VRPs); we have now compared an efficient polyethylenimine (PEI)-based formulation (polyplex) with VRP-delivery as well as naked RepRNA co-administered with the potent bis-(3',5')-cyclic dimeric adenosine monophosphate (c-di-AMP) adjuvant. All formulations contained a Rep-HA/Rep-NP mix, to assess the breadth of both humoral and cell-mediated defences against the influenza virus antigens. Assessment employed pigs for their close immunological relationship to humans, and as natural hosts for influenza virus. Animals receiving the VRPs, as well as PEI-delivered RepRNA, displayed strong humoral and cellular responses against both HA and NP, but with VRPs proving to be more efficacious. In contrast, naked RepRNA plus c-di-AMP could induce only low-level immune responses, in one out of five pigs. In conclusion, RepRNA encoding different influenza virus antigens are efficacious for inducing both humoral and cellular immune defences in pigs. Comparisons showed that packaging within VRP remains the most efficacious for delivery leading to induction of immune defences; however, this technology necessitates employment of expensive complementing cell cultures, and VRPs do not target human cells. Therefore, choosing the appropriate synthetic delivery vehicle still offers potential for rapid vaccine design, particularly in the context of the current coronavirus pandemic.

Edler, C., et al. (2021). "Deaths associated with newly launched SARS-CoV-2 vaccination (Comirnaty(R))." Leg Med (Tokyo) **51**: 101895.

Since 27th December 2020, a mRNA vaccine from BioNTech / Pfizer (Comirnaty(R)) has been used across Germany. As of 12th March 2021, 286 fatalities of vaccinated German individuals were registered at the Paul-Ehrlich-Institute with time intervals after vaccination between one hour to 40 days. From our catchment area in northern Germany, we have so far become aware of 22 deaths in connection with vaccination in a 5 week period (range: 0-28 days after vaccination). Three death cases after vaccination with Comirnaty(R), which were autopsied at the Institute of Legal Medicine Hamburg, are presented in more detail. All three deceased had severe cardiovascular diseases, among other comorbidities, and died in the context of these pre-existing conditions, while one case developed a COVID-19 pneumonia as cause of death. Taking into account the results of the postmortem examination a causal relation between the vaccination and the death was not established in any case. If there are indications of an allergic reaction, histological and postmortem laboratory examinations should be performed subsequent to the autopsy (tryptase, total IgE, CRP, interleukin-6, complement activity C3/C5).

Eifer, M., et al. (2021). "Covid-19 mRNA Vaccination: Age and Immune Status and its Association with Axillary Lymph Node PET/CT Uptake." J Nucl Med.

With hundreds of millions of coronavirus disease 2019 (COVID-19) mRNA-based vaccine doses planned to be delivered worldwide in the upcoming months, it is important to recognize positron emission tomography with computed tomography (PET/CT) findings in recently vaccinated immunocompetent or immunocompromised patients. We aimed to assess PET/CT uptake in the deltoid muscle and axillary

lymph nodes of patients that received a COVID-19 mRNA-based vaccine, and to evaluate its association with patients' age and immune status. Methods: All consecutive adult subjects undergoing PET/CT scans with any radiotracer at our center during the first month of a national COVID-19 vaccination rollout (between 23 December 2020 and January 27, 2021) were included. Data regarding clinical status, laterality and time interval from recent COVID-19 mRNA vaccination was prospectively collected and retrospectively analyzed, and correlated with deltoid muscle and axillary lymph nodes uptake. Results: Of 426 eligible, recently vaccinated, subjects (median age, 67+/-12 years; 49% female), 377 (88%) underwent PET/CT with F-18-fluorodeoxyglucose (FDG) and positive axillary lymph node uptake was seen in 45% of them. Multivariate logistic regression analysis revealed a strong inverse association between positive FDG uptake in ipsilateral lymph nodes and patients' age (Odds Ratio [OR]=0.57, 95% CI, 0.45-0.72; p<.001), immunosuppressive treatment (OR=0.37, 95% CI, 0.20-0.64; P = 0.003) and presence of hematological disease (OR=0.44, 95% CI, 0.24-0.8; P = 0.021). No such association was found for deltoid muscle uptake. The number of days from the last vaccination and the number of vaccination doses were also significantly associated with increased odds of positive lymph nodes uptake. Conclusion: Following mRNA-based COVID-19 vaccination, a high proportion of patients showed ipsilateral lymph node axillary uptake, which was more common in immunocompetent patients. This information will help recognize PET/CT pitfalls and may hint about the patient's immune response to the vaccine.

Elia, U., et al. (2021). "Design of SARS-CoV-2 hFc-Conjugated Receptor-Binding Domain mRNA Vaccine Delivered via Lipid Nanoparticles." ACS Nano.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the causal agent of COVID-19 and stands at the center of the current global human pandemic, with death toll exceeding one million. The urgent need for a vaccine has led to the development of various immunization approaches. mRNA vaccines represent a cell-free, simple, and rapid platform for immunization, and therefore have been employed in recent studies toward the development of a SARS-CoV-2 vaccine. Herein, we present the design of an mRNA vaccine, based on lipid nanoparticles (LNPs)-encapsulated SARS-CoV-2 human Fc-conjugated receptor-binding domain (RBD-hFc). Several ionizable lipids have been evaluated in vivo in a luciferase (luc) mRNA reporter assay, and two leading LNPs formulations have been chosen for the subsequent RBD-hFc mRNA vaccine strategy. Intramuscular administration of LNP RBD-hFc mRNA elicited robust humoral response, a high level of neutralizing antibodies and a Th1-biased cellular response in BALB/c mice. The data in the current study demonstrate the potential of these lipids as promising candidates for LNP-based mRNA vaccines in general and for a COVID19 vaccine in particular.

Erdeljic Turk, V. (2021). "Anaphylaxis associated with the mRNA COVID-19 vaccines: Approach to allergy investigation." Clin Immunol **227**: 108748.

Reports about cases of anaphylaxis to mRNA vaccines have created anxiety in the community and could increase vaccine hesitancy in the population. There are no standardized protocols for allergy testing to mRNA vaccines. PEG is currently the only excipient in both vaccines with recognized allergenic potential. Allergy to PEG has been reported with increasing frequency over recent years, often in patients who had repeated systemic allergic reactions/anaphylaxis to several classes of drugs before diagnosis. Proposed protocols are based on current knowledge about potential mechanisms of anaphylaxis associated with the mRNA vaccines, and the assumption that polyethylene glycol (PEG) is the most likely culprit. Allergy testing to PEGs and mRNA vaccines is complex and carries the risk of anaphylaxis and should be conducted in a specialist drug allergy center. Appropriate PEG-free emergency medical treatment and supervision should be readily available.

Fallet, B., et al. (2021). "[COVID-19 vaccines: vaccine targets, immunogenicity and allergic reactions]." Rev Med Suisse **17**(733): 690-696.

Many vaccine strategies have been developed to control the COVID-19 pandemic. This article presents the mechanisms of action and the efficacy of different vaccines including mRNA- and adenovirus-based vaccines. We will discuss the different vaccine targets, immune responses and allergic reactions which have been reported during the vaccination campaigns. Finally, the latest recommendations for the prevention and management of severe allergic reactions will be summarized.

Garcia-Beltran, W. F., et al. (2021). "Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity." Cell **184**(9): 2372-2383 e2379.

Vaccination elicits immune responses capable of potently neutralizing SARS-CoV-2. However, ongoing surveillance has revealed the emergence of variants harboring mutations in spike, the main target of neutralizing antibodies. To understand the impact of these variants, we evaluated the neutralization potency of 99 individuals that received one or two doses of either BNT162b2 or mRNA-1273 vaccines against

pseudoviruses representing 10 globally circulating strains of SARS-CoV-2. Five of the 10 pseudoviruses, harboring receptor-binding domain mutations, including K417N/T, E484K, and N501Y, were highly resistant to neutralization. Cross-neutralization of B.1.351 variants was comparable to SARS-CoV and bat-derived WIV1-CoV, suggesting that a relatively small number of mutations can mediate potent escape from vaccine responses. While the clinical impact of neutralization resistance remains uncertain, these results highlight the potential for variants to escape from neutralizing humoral immunity and emphasize the need to develop broadly protective interventions against the evolving pandemic.

Garcia-Montero, C., et al. (2021). "An Updated Review of SARS-CoV-2 Vaccines and the Importance of Effective Vaccination Programs in Pandemic Times." Vaccines (Basel) **9**(5).

Since the worldwide COVID-19 pandemic was declared a year ago, the search for vaccines has become the top priority in order to restore normalcy after 2.5 million deaths worldwide, overloaded sanitary systems, and a huge economic burden. Vaccine development has represented a step towards the desired herd immunity in a short period of time, owing to a high level of investment, the focus of researchers, and the urge for the authorization of the faster administration of vaccines. Nevertheless, this objective may only be achieved by pursuing effective strategies and policies in various countries worldwide. In the present review, some aspects involved in accomplishing a successful vaccination program are addressed, in addition to the importance of vaccination in a pandemic in the face of unwillingness, conspiracy theories, or a lack of information among the public. Moreover, we provide some updated points related to the landscape of the clinical development of vaccine candidates, specifically, the top five vaccines that are already being assessed in Phase IV clinical trials (BNT162b2, mRNA-1273, AZD1222, Ad26.COV2.S, and CoronaVac).

Giavina-Bianchi, P. and J. Kalil (2021). "May polyethylene glycol be the cause of anaphylaxis to mRNA COVID-19 vaccines?" World Allergy Organ J **14**(4): 100532.

Vaccination against coronavirus is essential to minimize the impact of the COVID-19 pandemic. Rare cases of anaphylaxis associated with the mRNA COVID-19 vaccines are being described, and the mechanisms involved in these reactions are poorly understood. A potential culprit agent of these vaccine-induced anaphylaxis events is polyethylene glycol, which has been reported as a cause of anaphylaxis. However, a cause-effect association has not been demonstrated, and the cases of anaphylaxis to mRNA COVID-19 vaccines should be further investigated. In this scenario, the recommendations are inaccurate and can lead to misinterpretation. At the moment, a more accurate recommendation would be the contraindication of mRNA COVID-19 vaccines in patients with immediate hypersensitivity reaction to polyethylene glycol or polysorbate. Patients with history of anaphylaxis to other or unknown causes should be referred to an allergist-immunologist for further orientation.

Goel, R. R., et al. (2021). "Distinct antibody and memory B cell responses in SARS-CoV-2 naive and recovered individuals following mRNA vaccination." Sci Immunol **6**(58).

Novel mRNA vaccines for SARS-CoV-2 have been authorized for emergency use. Despite their efficacy in clinical trials, data on mRNA vaccine-induced immune responses are mostly limited to serological analyses. Here, we interrogated antibody and antigen-specific memory B cells over time in 33 SARS-CoV-2 naive and 11 SARS-CoV-2 recovered subjects. SARS-CoV-2 naive individuals required both vaccine doses for optimal increases in antibodies, particularly for neutralizing titers against the B.1.351 variant. Memory B cells specific for full-length spike protein and the spike receptor binding domain (RBD) were also efficiently primed by mRNA vaccination and detectable in all SARS-CoV-2 naive subjects after the second vaccine dose, though the memory B cell response declined slightly with age. In SARS-CoV-2 recovered individuals, antibody and memory B cell responses were significantly boosted after the first vaccine dose; however, there was no increase in circulating antibodies, neutralizing titers, or antigen-specific memory B cells after the second dose. This robust boosting after the first vaccine dose strongly correlated with levels of pre-existing memory B cells in recovered individuals, identifying a key role for memory B cells in mounting recall responses to SARS-CoV-2 antigens. Together, our data demonstrated robust serological and cellular priming by mRNA vaccines and revealed distinct responses based on prior SARS-CoV-2 exposure, whereby COVID-19 recovered subjects may only require a single vaccine dose to achieve peak antibody and memory B cell responses. These findings also highlight the utility of defining cellular responses in addition to serologies and may inform SARS-CoV-2 vaccine distribution in a resource-limited setting.

Goel, R. R., et al. (2021). "Longitudinal Analysis Reveals Distinct Antibody and Memory B Cell Responses in SARS-CoV2 Naive and Recovered Individuals Following mRNA Vaccination." medRxiv.

Novel mRNA vaccines for SARS-CoV2 have been authorized for emergency use and are currently being administered to millions of individuals worldwide. Despite their efficacy in clinical trials, there is limited data on vaccine-induced immune responses in individuals with a prior SARS-CoV2 infection compared to SARS-CoV2 naive subjects. Moreover, how mRNA vaccines impact the development of antibodies as well as memory B cells in COVID-19 experienced versus COVID-19 naive subjects remains poorly understood. In this study, we evaluated antibody responses and antigen-specific memory B cell responses over time in 33 SARS-CoV2 naive and 11 SARS-CoV2 recovered subjects. mRNA vaccination induced significant antibody and memory B cell responses against full-length SARS-CoV2 spike protein and the spike receptor binding domain (RBD). SARS-CoV2 naive individuals benefitted from both doses of mRNA vaccine with additional increases in antibodies and memory B cells following booster immunization. In contrast, SARS-CoV2 recovered individuals had a significant immune response after the first dose with no increase in circulating antibodies or antigen-specific memory B cells after the second dose. Moreover, the magnitude of the memory B cell response induced by vaccination was lower in older individuals, revealing an age-dependence to mRNA vaccine-induced B cell memory. Side effects also tended to associate with post-boost antibody levels, but not with post-boost memory B cells, suggesting that side effect severity may be a surrogate of short-term antibody responses. The frequency of pre-vaccine antigen-specific memory B cells in SARS-CoV2 recovered individuals strongly correlated with post-vaccine antibody levels, supporting a key role for memory B cells in humoral recall responses to SARS-CoV2. This observation may have relevance for future booster vaccines and for responses to viral variants that partially escape pre-existing antibodies and require new humoral responses to be generated from memory B cells. Finally, post-boost antibody levels were not correlated with post-boost memory responses in SARS-CoV2 naive individuals, indicating that short-term antibody levels and memory B cells are complementary immunological endpoints that should be examined in tandem when evaluating vaccine response. Together, our data provide evidence of both serological response and immunological memory following mRNA vaccination that is distinct based on prior SARS-CoV2 exposure. These findings may inform vaccine distribution in a resource-limited setting. Abstract Figure:

Golob, J. L., et al. (2021). "SARS-CoV-2 vaccines: a triumph of science and collaboration." JCI Insight.

Roughly one year after the first case of COVID-19 was identified and less than one year after the sequencing of SARS-CoV-2, multiple SARS-CoV-2 vaccines with demonstrated safety and efficacy in phase III clinical trials are available. The most promising vaccines have targeted the surface glycoprotein (S-protein) of SARS-CoV-2 and achieved an approximate 85-95% reduction in the risk of symptomatic COVID-19, while retaining excellent safety profiles and modest side effects in the phase III clinical trials. The mRNA, replication-incompetent viral vector, and protein subunit vaccine technologies have all been successfully employed. Some novel SARS-CoV-2 variants evade but do not appear to fully overcome the potent immunity induced by these vaccines. Emerging real-world effectiveness data add evidence for protection from severe COVID-19. This is an impressive first demonstration of the effectiveness of the mRNA vaccine and vector vaccine platforms. The success of SARS-CoV-2 vaccine development should be credited to open science, industry partnerships, harmonization of clinical trials, and the altruism of study participants. The manufacturing and distribution of the emergency use-authorized SARS-CoV-2 vaccines are ongoing challenges. What remains now is to ensure broad and equitable global vaccination against COVID-19. .

Gordon, J., et al. (2021). "An Informative Discussion for School Nurses on COVID-19 mRNA Vaccine." NASN Sch Nurse **36**(3): 132-136.

School nurses are advocates, caregivers, and teachers. It is the responsibility of school nurses to understand current prevention and treatment options. In understanding how and why coronavirus disease 2019 (COVID-19) mRNA vaccines work, school nurses are in a trusted position to explain and advocate vaccination to students and their caregivers. The messenger ribonucleic acid (mRNA) vaccine is a product of the latest scientific and medical technology. A better understanding of how and why this vaccination is effective may prevent vaccination hesitancy and provide reassurance to those choosing to accept vaccination. In December 2020, the National Association of School Nurses publicized its support for vaccination against COVID-19. As the COVID-19 pandemic lingers school nurses will step toward the front line to aid in the abatement of poor public health outcomes that may be severely affecting their schools, students, and caregivers.

Goswami, R., et al. (2021). "Conjugation of Mannans to Enhance the Potency of Liposome Nanoparticles for the Delivery of RNA Vaccines." Pharmaceutics **13**(2).

Recent approval of mRNA vaccines to combat COVID-19 have highlighted the potential of this platform. Lipid nanoparticles (LNP) is the delivery

vehicle of choice for mRNA as they prevent its enzymatic degradation by encapsulation. We have recently shown that surface exposition of mannose, incorporated in LNPs as stable cholesterol-amine conjugate, enhances the potency of self-amplifying RNA (SAM) replicon vaccines through augmented uptake by antigen presenting cells (APCs). Here, we generated a new set of LNPs whose surface was modified with mannans of different length (from mono to tetrasaccharide), in order to study the effect on antibody response of model SAM replicon encoding for the respiratory syncytial virus fusion F protein. Furthermore, the impact of the mannosylated liposomal delivery through intradermal as well as intramuscular routes was investigated. The vaccine priming response showed to improve consistently with increase in the chain length of mannoses; however, the booster dose response plateaued above the length of disaccharide. An increase in levels of IgG1 and IgG2a was observed for mannnosylated lipid nanoparticles (MLNPs) as compared to LNPs. This work confirms the potential of mannosylated SAM LNPs for both intramuscular and intradermal delivery, and highlights a disaccharide length as sufficient to ensure improved immunogenicity compared to the un-glycosylated delivery system.

Gotkin, R. H., et al. (2021). "Global Recommendations on COVID-19 Vaccines and Soft Tissue Filler Reactions: A Survey-Based Investigation in Cooperation With the International Society for Dermatologic and Aesthetic Surgery (ISDS)." J Drugs Dermatol **20**(4): 374-378.

BACKGROUND: Recent reports have surfaced from the United States Food and Drug Administration hearings in December 2020 regarding the COVID-19 vaccines and study participants who developed facial and/or lip swelling after receiving the newly developed drug. Despite an incidence rate of 0.02% in the vaccine arm of the Moderna mRNA-1273 trial, concerns have been expressed about the association of adverse reactions following soft tissue filler injections and the COVID-19 vaccines. The International Society for Dermatologic and Aesthetic Surgery (ISDS) understands these concerns and has designed the following study. METHODS: A global survey was designed to capture the incidence of adverse events related to: (1) previous soft tissue filler injections, (2) soft tissue filler injections during positive testing for COVID-19, and (3) soft tissue filler injections during and after receiving any of the COVID-19 vaccines globally available. RESULTS: The information of 106 survey participants from 18 different countries was analyzed. 80.2% (n=85) never experienced any adverse reaction following their soft tissue filler injection whereas 15.1% (n=16) experienced swelling and 4.7% (n=5) experienced pain that lasted longer than two days. Of those who received at least one dose of the COVID-19 vaccine (n=78), 94.9% reported not to have experienced any adverse reaction related to their previous soft tissue filler injection, whereas 5.1% (n=4) reported to have perceived pain that lasted longer than two days. CONCLUSION: The data collected does not support the concern for an increased risk of developing adverse reactions following soft tissue filler injections associated with the COVID-19 vaccines compared to that risk associated with other previously described triggers or the default risk following soft tissue filler injections. J Drugs Dermatol. 20(4):374-378. doi:10.36849/JDD.2021.6041.

Grupper, A., et al. (2021). "Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus." Am J Transplant.

COVID-19 is associated with increased morbidity and mortality in transplant recipients. There are no efficacy data available regarding these patients with any of the available SARS-CoV-2 vaccines. We analyzed the humoral response following full vaccination with the BNT162b2 (Pfizer-BioNTech) in 136 kidney transplant recipients, and compared it to 25 controls. In order to exclude prior exposure to the virus, only participants with negative serology to SARS-CoV-2 nucleocapsid protein were included. All controls developed a positive response to spike protein, while only 51 of 136 transplant recipients (37.5%) had positive serology ($p < .001$). Mean IgG anti-spike level was higher in the controls (31.05 [41.8] vs. 200.5 [65.1] AU/mL, study vs. control, respectively, $p < .001$). Variables associated with null humoral response were older age (odds ratio 1.66 [95% confidence interval 1.17-2.69]), high-dose corticosteroids in the last 12 months (1.3 [1.09-1.86]), maintenance with triple immunosuppression (1.43 [1.06-2.15]), and regimen that includes mycophenolate (1.47 [1.26-2.27]). There was a similar rate of side effects between controls and recipients, and no correlation was found between the presence of symptoms and seroconversion. Our findings suggest that most kidney transplant recipients remain at high risk for COVID-19 despite vaccination. Further studies regarding possible measures to increase recipient's response to vaccination are required.

Gyanwali, P., et al. (2020). "Safety and Efficacy of Different Therapeutic Interventions on Prevention and Treatment of COVID-19." J Nepal Health Res Counc **18**(2): 151-158.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of coronavirus that causes coronavirus disease 2019

(COVID-19), a respiratory illness. COVID-19 has now become a global public health crisis causing alarming numbers of morbidity and mortality. Ever since the COVID-19 pandemic started scientists, researchers, universities, companies, and institutions all around the world have been endeavoring to discover a potential treatment for COVID-19. Numerous studies and clinical trials on vaccines and drugs for the prevention and treatment of COVID-19 are underway across the world. However, the uncertainty around the efficacy and safety of various treatment regimens have become one of the biggest challenges in the battle against the SARS-CoV-2. This paper is a narrative review of articles regarding the various treatments and vaccines being tested for the SARS-CoV-2, available in the PubMed database along with Google Scholar. There are ongoing clinical trials on potential drugs such as remdesivir, favipiravir, lopinavir/ritonavir, chloroquine, and hydroxychloroquine, corticosteroids tocilizumab, azithromycin, anakinra, etc. and other therapeutic modalities like convalescent plasma therapy. Likewise, vaccines against SARS-CoV-2 are being developed and tested, including mRNA, non-replicating viral vector, DNA, protein subunit candidate vaccines, etc. Although some early-stage clinical trials and studies on these drugs and vaccines have shown positive results, definitive and conclusive results are yet to be obtained. Keywords: COVID-19; antiviral drugs; COVID-19 treatment; COVID-19 vaccine; SARS-CoV-2.

Hachim, M. Y., et al. (2020). "Interferon-Induced Transmembrane Protein (IFITM3) Is Upregulated Explicitly in SARS-CoV-2 Infected Lung Epithelial Cells." Front Immunol **11**: 1372.

Current guidelines for COVID-19 management recommend the utilization of various repurposed drugs. Despite ongoing research toward the development of a vaccine against SARS-CoV-2, such a vaccine will not be available in time to contribute to the containment of the ongoing pandemic. Therefore, there is an urgent need to develop a framework for the rapid identification of novel targets for diagnostic and therapeutic interventions. We analyzed publicly available transcriptomic datasets of SARS-CoV infected humans and mammals to identify consistent differentially expressed genes then validated in SARS-CoV-2 infected epithelial cells transcriptomic datasets. Comprehensive toxicogenomic analysis of the identified genes to identify possible interactions with clinically proven drugs was carried out. We identified IFITM3 as an early upregulated gene, and valproic acid was found to enhance its mRNA expression as well as induce its antiviral action. These findings indicate that analysis of publicly available transcriptomic and toxicogenomic data represents a rapid approach for the identification of novel targets and molecules that can modify the action of such targets during the early phases of emerging infections like COVID-19.

Hajissa, K. and A. Mussa (2021). "Positive aspects of the mRNA platform for SARS-CoV-2 vaccines." Hum Vaccin Immunother: 1-3.

The unprecedented need to acquire a safe and effective vaccine for the long-term control of coronavirus disease 2019 (COVID-19) is a global imperative. Researchers have been working urgently and collaboratively to develop vaccines against the causative agent of COVID-19. The use of messenger RNA (mRNA) vaccine platform offers new opportunities for the development of effective vaccines. The first use of COVID-19 mRNA vaccines for individuals outside the clinical trials raised concerns over their safety and future efficacy. In social media, particularly in developing countries, widely shared false claims allege that the current mRNA-based COVID-19 vaccines potentially integrate into the host genome and thus may genetically modify humans. These vaccines are also assumed to lack efficacy due to the emergence of new strains. Such misinformation cause people to hesitate about receiving vaccination against COVID-19. This commentary aimed to outline the structure, mechanism of action and the major motive for the use of COVID-19 mRNA vaccine, with a focus on scientifically addressing challenges associated with conspiracy theories and dispelling misinformation around vaccination.

Hao, L. T., et al. (2021). "Tamper-Proof Time-Temperature Indicator for Inspecting Ultracold Supply Chain." ACS Omega **6**(12): 8598-8604.

In the precarious situation caused by the COVID-19 pandemic, the use of messenger ribonucleic acid (mRNA) vaccines is promising for prevention against the infection. However, this type of vaccine has not been effectively commercialized because it needs to be stored and transported at ultracold conditions. mRNA vaccines exposed to undesired temperatures may not show any visible changes but can deteriorate and cause negative effects. Consumers' demand for vaccine authenticity requires logistics to develop a robust monitoring tool to ensure the integrity of ultracold supply chain from manufacturing until vaccination. Here, we report a time-temperature indicator (TTI) that can detect a relatively small change in temperature within subzero ranges, for example, from -70 to -60 degrees C, which cannot be achieved by current TTIs operating at room temperature. A dyed noneutectic ethylene glycol/water mixture that melts near the mRNA conservation temperature (-69 degrees C) diffuses into a white absorbent and leaves a colored trace. In addition, the heterogeneous ice particles in the noneutectic mobile phase can prevent absorption

during short-term exposure to room temperature. Therefore, the proposed TTI will not record inevitable "meaningless" short-term exposure to room temperature during the cold supply chain but monitor the "meaningful" relatively long-term exposure above -60 degrees C. These findings help facilitate the safe distribution of the COVID-19 mRNA vaccines.

Haq, E. U., et al. (2020). "Frontiers in the COVID-19 vaccines development." Exp Hematol Oncol **9**: 24.

Novel corona virus caused pneumonia first reported in December, 2019 in Wuhan, China was later named COVID-19. Due to its special pathogenicity, COVID-19 transmitted with high speed beyond borders and has significantly affected normal life. Currently, no specific drugs, treatment or vaccines are available. Vaccine development for COVID-19 is a highly complex process involving viral genomic studies, identification of target for vaccine, vaccine design, manufacturing, storage and distribution, preclinical and clinical safety and efficacy studies. The high levels of efforts and global collaboration at this scale is unprecedented. The World Health Organization (WHO) has documented 160 different COVID-19 vaccine candidates as of July 13, 2020 with 26 currently on clinical evaluation while 137 vaccines on preclinical evaluation. COVID-19 vaccine efforts mark the first use of mRNA-type vaccines ever evaluated. Numerous research organizations have successfully initiated clinical evaluation of COVID-19 vaccines. This review aims to summarize the advances and challenges for COVID-19 vaccines development.

Hassert, M., et al. (2020). "mRNA induced expression of human angiotensin-converting enzyme 2 in mice for the study of the adaptive immune response to severe acute respiratory syndrome coronavirus 2." PLoS Pathog **16**(12): e1009163.

The novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic. Critical to the rapid evaluation of vaccines and antivirals against SARS-CoV-2 is the development of tractable animal models to understand the adaptive immune response to the virus. To this end, the use of common laboratory strains of mice is hindered by significant divergence of the angiotensin-converting enzyme 2 (ACE2), which is the receptor required for entry of SARS-CoV-2. In the current study, we designed and utilized an mRNA-based transfection system to induce expression of the hACE2 receptor in order to confer entry of SARS-CoV-2 in otherwise non-permissive cells. By employing this expression system in an in vivo setting, we were able to interrogate the adaptive immune response to SARS-CoV-2 in type 1 interferon receptor deficient mice. In doing so, we showed that the T cell response to SARS-CoV-2 is enhanced when hACE2 is expressed during infection. Moreover, we demonstrated that these responses are preserved in memory and are boosted upon secondary infection. Importantly, using this system, we functionally identified the CD4+ and CD8+ structural peptide epitopes targeted during SARS-CoV-2 infection in H2b restricted mice and confirmed their existence in an established model of SARS-CoV-2 pathogenesis. We demonstrated that, identical to what has been seen in humans, the antigen-specific CD8+ T cells in mice primarily target peptides of the spike and membrane proteins, while the antigen-specific CD4+ T cells target peptides of the nucleocapsid, membrane, and spike proteins. As the focus of the immune response in mice is highly similar to that of the humans, the identification of functional murine SARS-CoV-2-specific T cell epitopes provided in this study will be critical for evaluation of vaccine efficacy in murine models of SARS-CoV-2 infection.

Heine, G. H., et al. (2021). "[SARS-CoV-2 vaccines - what the nephrologist should know]." Dtsch Med Wochenschr **146**(7): 466-470.

Only fifteen months after the beginning of the COVID-19 pandemic, several vaccines are already available for clinical use. While the spike protein of SARS-CoV-2 constitutes the main target of all predominant SARS-CoV-2 vaccines, they work by different mechanisms (mRNA-based vaccines vs. vector-based vaccines vs. protein-based vaccines).Though there are slight differences regarding the level of protection against mild COVID-19, all five vaccines that have been through phase 3 trials were nearly 100 % effective in preventing severe or fatal cases of COVID-19. The side effects were of short duration.Patients with chronic kidney disease (or other significant comorbidities) were largely excluded from Phase 3 trials, which makes definite recommendations concerning their vaccination difficult. The vaccine's effectiveness may be reduced in that population due to a uremic immune defect and/or immunosuppressive medication. However, these patients have an increased risk for severe or fatal COVID-19, so that they may particularly benefit from the vaccine.

Hernandez, A. F., et al. (2021). "Safety of COVID-19 vaccines administered in the EU: Should we be concerned?" Toxicol Rep **8**: 871-879.

The COVID-19 pandemic has had an unprecedented and devastating impact on public health, society and economics around the world. As a result, the development of vaccines to protect individuals from symptomatic COVID-19 infections has represented the only feasible health tool to combat the spread of the disease. However, at the same time the development and regulatory assessment of different

vaccines has challenged pharmaceutical industries and regulatory agencies as this process has occurred in the shorter time ever though. So far, two mRNA and two adenovirus-vectored vaccines have received a conditional marketing authorisation in the EU and other countries. This review summarized and discusses the assessment reports of the European Medicine Agency (EMA) concerning the safety of the 3 vaccines currently used in the EU (Pfizer, Moderna and Astra-Zeneca). A particular focus has been paid to safety information from pre-clinical (animal) and clinical (phase 3 trials) studies. Overall, the most frequent adverse effects reported after the administration of these vaccines consisted of local reactions at the injection site (sore arm and erythema) followed by non-specific systemic effects (myalgia, chills, fatigue, headache, and fever), which occurred soon after vaccination and resolved shortly. Rare cases of vaccine-induced immune thrombotic thrombocytopenia have been reported for Vaxzevria. Data on long-term studies, interaction with other vaccines, use in pregnancy/breast-feeding, use in immunocompromised subjects, and in subjects with comorbidities, autoimmune or inflammatory disorders are still missing for these vaccines. Therefore, careful follow-up and surveillance studies for continued vaccine safety monitoring will be needed to ascertain the potential risks of such adverse events or diseases. In conclusion, the benefits and risks of current COVID-19 vaccines must be weighed against the real possibility of contract the disease and develop complications and long-term sequels; all this on the basis of the available scientific evidence and in the absence of unmotivated biases.

Ho, D. (2020). "Addressing COVID-19 Drug Development with Artificial Intelligence." Adv Intell Syst: 2000070.

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that led to the COVID-19 (Coronavirus Disease 2019) pandemic, has resulted in substantial overburdening of healthcare systems as well as an economic crisis on a global scale. This has in turn resulted in widespread efforts to identify suitable therapies to address this aggressive pathogen. Therapeutic antibody and vaccine development are being actively explored, and a phase I clinical trial of mRNA-1273 which is developed in collaboration between the National Institute of Allergy and Infectious Diseases and Moderna, Inc. is currently underway. Timelines for the broad deployment of a vaccine and antibody therapies have been estimated to be 12-18 months or longer. These are promising approaches that may lead to sustained efficacy in treating COVID-19. However, its emergence has also led to a large number of clinical trials evaluating drug combinations composed of repurposed therapies. As study results of these combinations continue to be evaluated, there is a need to move beyond traditional drug screening and repurposing by harnessing artificial intelligence (AI) to optimize combination therapy design. This may lead to the rapid identification of regimens that mediate unexpected and markedly enhanced treatment outcomes.

Jackson, L. A., et al. (2020). "An mRNA Vaccine against SARS-CoV-2 - Preliminary Report." N Engl J Med **383**(20): 1920-1931.

BACKGROUND: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and spread globally, prompting an international effort to accelerate development of a vaccine. The candidate vaccine mRNA-1273 encodes the stabilized prefusion SARS-CoV-2 spike protein. METHODS: We conducted a phase 1, dose-escalation, open-label trial including 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 mug, 100 mug, or 250 mug. There were 15 participants in each dose group. RESULTS: After the first vaccination, antibody responses were higher with higher dose (day 29 enzyme-linked immunosorbent assay anti-S-2P antibody geometric mean titer [GMT], 40,227 in the 25-mug group, 109,209 in the 100-mug group, and 213,526 in the 250-mug group). After the second vaccination, the titers increased (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively). After the second vaccination, serum-neutralizing activity was detected by two methods in all participants evaluated, with values generally similar to those in the upper half of the distribution of a panel of control convalescent serum specimens. Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-mug dose group reported one or more severe adverse events. CONCLUSIONS: The mRNA-1273 vaccine induced anti-SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified. These findings support further development of this vaccine. (Funded by the National Institute of Allergy and Infectious Diseases and others; mRNA-1273 ClinicalTrials.gov number, NCT04283461).

Jahn, M., et al. (2021). "Humoral Response to SARS-CoV-2-Vaccination with BNT162b2 (Pfizer-BioNTech) in Patients on Hemodialysis." Vaccines (Basel) **9**(4).

mRNA-based SARS-CoV-2 vaccines offer a preventive strategy against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections that is of interest in the care of patients on hemodialysis

(HDP). We measured humoral immune responses in 72 HDP after standard vaccination with two doses of the mRNA-based SARS-CoV-2 vaccine BNT162b2 (Pfizer-BioNTech). Antibody responses were evaluated with an anti-SARS-CoV-2 IgG ChemiLuminescent ImmunoAssay (CLIA) two weeks after the second dose. In addition, SARS-CoV-2 IgG was determined in a control of 16 healthy healthcare workers (HCW). The control group of HCW has shown a strong antibody response with a median (MD (Q1; Q3)) antibody titer of 800.0 AU/mL (520.5; 800.0). In comparison to HCW, HDP under 60 years of age responded equally (597.0 AU/mL (410.5; 800.0), $p = 0.051$). However, the antibody responses of the HDP negatively correlated with age ($r(2) = 0.2954$ $p < 0.0001$), leading to significantly lower antibody titers in HDP over 60 years (280.0 AU/mL (45.7; 477.0), $p < 0.0001$). To thoroughly understand the immunogenicity of the new mRNA-based vaccines in HDP, longitudinal data on the effectiveness and durability of antibody responses are needed. Modifications of immunization schedules should be considered in HDP with low or without antibody responsiveness after standard vaccination to boost immune reactivity and prolong protective effects in these vulnerable patients.

Jones, N. K., et al. (2021). "Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection." Elife **10**.

The BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) is being utilised internationally for mass COVID-19 vaccination. Evidence of single-dose protection against symptomatic disease has encouraged some countries to opt for delayed booster doses of BNT162b2, but the effect of this strategy on rates of asymptomatic SARS-CoV-2 infection remains unknown. We previously demonstrated frequent pauci- and asymptomatic SARS-CoV-2 infection amongst healthcare workers (HCWs) during the UK's first wave of the COVID-19 pandemic, using a comprehensive PCR-based HCW screening programme (Rivett et al., 2020; Jones et al., 2020). Here, we evaluate the effect of first-dose BNT162b2 vaccination on test positivity rates and find a fourfold reduction in asymptomatic infection amongst HCWs >/=12 days post-vaccination. These data provide real-world evidence of short-term protection against asymptomatic SARS-CoV-2 infection following a single dose of BNT162b2 vaccine, suggesting that mass first-dose vaccination will reduce SARS-CoV-2 transmission, as well as the burden of COVID-19 disease.

Jung, J. (2021). "Preparing for the Coronavirus Disease (COVID-19) Vaccination: Evidence, Plans, and Implications." J Korean Med Sci **36**(7): e59.

The formation of herd immunity through vaccination is a key point in overcoming the coronavirus disease 2019 (COVID-19) pandemic. To acquire herd immunity, a high vaccination rate is required, which is necessary to instill confidence in the public regarding the effectiveness and safety of the vaccine. In the real-world setting, thorough preparation of components, such as priority setting, vaccine delivery, logistics, and side-effect monitoring is necessary to overcome vaccine hesitancy. Each country prioritizes vaccination since healthcare workers, nursing facility residents, and the elderly population, and similar trends are found between countries. Vaccination is performed at large centers and medical institutions operated by the country, and variations are dependent on the environment of each country. The transport of mRNA vaccines is a challenging task, and to this end, each government is striving for safe distribution. In addition, each authority operates a surveillance system to monitor the safety of vaccines, and Korea needs to produce evidence for monitoring effects and side effects with expertise. Even after the acquisition of herd immunity, COVID-19 is highly likely to remain an endemic infectious disease, and a higher immunity level may be required because of variants of the virus. If the spread of variants of concern continues, a booster vaccination may be required. Therefore, non-pharmaceutical interventions, such as social distancing, wearing a mask, and epidemiological investigation should be maintained.

Kadali, R. A. K., et al. (2021). "Non-life-threatening adverse effects with COVID-19 mRNA-1273 vaccine: A randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms." J Med Virol.

There are concerns regarding the side effects of the new coronavirus disease 2019 (COVID-19) mRNA-1273 vaccine among healthcare workers (HCWs) in the United States. The objective of the study was to investigate the side effects of the mRNA-1273 vaccine with detailed review of organ systems. A randomized, cross-sectional study using an independent online survey questionnaire was conducted to collect responses from HCWs. Of all participants, 87.8% (1116/1271) provided complete responses. Of them, 38.7% (432/1116) received the mRNA-1273 vaccine, among which, 89.35% were females; 425 of these 432 mRNA-1273 vaccine recipients (98.34%) reported at least one or more symptoms. The results were classified based on the frequency of symptoms reported postvaccination. Of these, 254/432 (58.8%) were able to continue their daily routine activities. 108/432 (25%) temporarily had trouble to perform daily activities, 120/432 (27.78%) required transient time off from work, 17/432 (3.94%) required help from an outpatient provider, 1/432 (0.23%) required help from emergency

department, and none of them were hospitalized. Despite the wide array of self-reported symptoms, 97.02% of the HCWs did not intend to skip the second dose of vaccine. Among all the symptoms reported, localized pain, generalized weakness, headache, myalgia, chills, fever, nausea, joint pains, sweating, localized swelling at the injection site, dizziness, itching, rash, decreased appetite, muscle spasm, decreased sleep quality, and brain fogging were the most commonly reported symptoms (in descending order of occurrence). Most of the symptoms reported were nonlife threatening. Despite the wide array of self-reported symptoms, there appears to be a higher acceptance for this vaccine.

Kadali, R. A. K., et al. (2021). "Side effects of BNT162b2 mRNA COVID-19 vaccine: A randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers." Int J Infect Dis **106**: 376-381.

INTRODUCTION: Concerns are prevailing about the safety and side effects of the BNT162b2 mRNA vaccine for coronavirus disease 2019 (COVID-19). METHODS: A randomized, cross-sectional study was performed to investigate the side effects of the BNT162b2 vaccine using an independent online questionnaire gathering responses from healthcare workers (HCWs) with detailed review of organ systems. RESULTS: Of all HCWs, 87.98% (1245/1415) completed the survey. Of them, 64.5% (803/1245) received the BNT162b2 mRNA vaccine and reported at least one or more symptoms (classified based on organ systems and occurrence rate) post vaccination. Of these, 640/803 (79.7%) were able to continue activities of daily living (ADL), 103/803 (12.83%) had trouble temporarily to perform ADL, 99/803 (12.33%) took time off work temporarily, 20/803 (2.49%) required help from an outpatient provider, 5/803 (0.62%) required help from an emergency department and 2/803 (0.25%) required hospitalization. Despite this, 97.61% intended to have the second dose and 92.9% had already received it. CONCLUSIONS: Commonly reported symptoms (occurrence in descending order) were soreness, fatigue, myalgia, headache, chills, fever, joint pain, nausea, muscle spasm, sweating, dizziness, flushing, feelings of relief, brain fogging, anorexia, localized swelling, decreased sleep quality, itching, tingling, diarrhoea, nasal stuffiness and palpitations. Despite this, remarkable acceptance for the second dose of the BNT162b2 vaccine was found among HCWs.

Kakodkar, P., et al. (2020). "A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19)." Cureus **12**(4): e7560.

Coronavirus disease 2019 (COVID-19) is a declared global pandemic. There are multiple parameters of the clinical course and management of the COVID-19 that need optimization. A hindrance to this development is the vast amount of misinformation present due to scarcely sourced manuscript preprints and social media. This literature review aims to presents accredited and the most current studies pertaining to the basic sciences of SARS-CoV-2, clinical presentation and disease course of COVID-19, public health interventions, and current epidemiological developments. The review on basic sciences aims to clarify the jargon in virology, describe the virion structure of SARS-CoV-2 and present pertinent details relevant to clinical practice. Another component discussed is the brief history on the series of experiments used to explore the origins and evolution of the phylogeny of the viral genome of SARS-CoV-2. Additionally, the clinical and epidemiological differences between COVID-19 and other infections causing outbreaks (SARS, MERS, H1N1) are elucidated. Emphasis is placed on evidence-based medicine to evaluate the frequency of presentation of various symptoms to create a stratification system of the most important epidemiological risk factors for COVID-19. These can be used to triage and expedite risk assessment. Furthermore, the limitations and statistical strength of the diagnostic tools currently in clinical practice are evaluated. Criteria on rapid screening, discharge from hospital and discontinuation of self-quarantine are clarified. Epidemiological factors influencing the rapid rate of spread of the SARS-CoV-2 virus are described. Accurate information pertinent to improving prevention strategies is also discussed. The penultimate portion of the review aims to explain the involvement of micronutrients such as vitamin C and vitamin D in COVID19 treatment and prophylaxis. Furthermore, the biochemistry of the major candidates for novel therapies is briefly reviewed and a summary of their current status in the clinical trials is presented. Lastly, the current scientific data and status of governing bodies such as the Center of Disease Control (CDC) and the WHO on the usage of controversial therapies such as angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) (Ibuprofen), and corticosteroids usage in COVID-19 are discussed. The composite collection of accredited studies on each of these subtopics of COVID-19 within this review will enable clarification and focus on the current status and direction in the planning of the management of this global pandemic.

Kalita, P., et al. (2020). "Design of a peptide-based subunit vaccine against novel coronavirus SARS-CoV-2." Microb Pathog **145**: 104236.

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that was first reported in Wuhan, China, and has subsequently spread worldwide. In the absence of any antiviral or immunomodulatory therapies, the disease is spreading at an alarming rate. A possibility of a resurgence of COVID-19 in places where lockdowns have already worked is also developing. Thus, for controlling COVID-19, vaccines may be a better option than drugs. An mRNA-based anti-COVID-19 candidate vaccine has entered a phase 1 clinical trial. However, its efficacy and potency have to be evaluated and validated. Since vaccines have high failure rates, as an alternative, we are presenting a new, designed multi-peptide subunit-based epitope vaccine against COVID-19. The recombinant vaccine construct comprises an adjuvant, cytotoxic T-lymphocyte (CTL), helper T-lymphocyte (HTL), and B-cell epitopes joined by linkers. The computational data suggest that the vaccine is non-toxic, non-allergenic, thermostable, with the capability to elicit a humoral and cell-mediated immune response. The stabilization of the vaccine construct is validated with molecular dynamics simulation studies. This unique vaccine is made up of 33 highly antigenic epitopes from three proteins that have a prominent role in host-receptor recognition, viral entry, and pathogenicity. We advocate this vaccine must be synthesized and tested urgently as a public health priority.

Kalra, R. S., et al. (2021). "COVID19-inhibitory activity of withanolides involves targeting of the host cell surface receptor ACE2: insights from computational and biochemical assays." J Biomol Struct Dyn: 1-14.

SARS-CoV-2 outbreak in China in December 2019 and its spread as worldwide pandemic has been a major global health crisis. Extremely high infection and mortality rate has severely affected all sectors of life and derailed the global economy. While drug and vaccine development have been prioritized and have made significant progression, use of phytochemicals and herbal constituents is deemed as a low-cost, safer and readily available alternative. We investigated therapeutic efficacy of eight withanolides (derived from Ashwagandha) against the angiotensin-converting enzyme 2 (ACE2) proteins, a target cell surface receptor for SARS-CoV-2 and report results on the (i) computational analyses including binding affinity and stable interactions with ACE2, occupancy of ACE2 residues in making polar and nonpolar interactions with different withanolides/ligands and (2) in vitro mRNA and protein analyses using human cancer (A549, MCF7 and HSC3) cells. We found that among all withanolides, Withaferin-A, Withanone, Withanoside-IV and Withanoside-V significantly inhibited the ACE2 expression. Analysis of withanolides-rich aqueous extracts derived from Ashwagandha leaves and stem showed a higher ACE2 inhibitory potency of stem-derived extracts. Taken together, we demonstrated the inhibitory potency of Ashwagandha withanolides and its aqueous extracts against ACE2.Communicated by Ramaswamy H. Sarma.

Karpinski, T. M., et al. (2021). "The 2020 race towards SARS-CoV-2 specific vaccines." Theranostics **11**(4): 1690-1702.

The global outbreak of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) highlighted a requirement for two pronged clinical interventions such as development of effective vaccines and acute therapeutic options for medium-to-severe stages of "coronavirus disease 2019" (COVID-19). Effective vaccines, if successfully developed, have been emphasized to become the most effective strategy in the global fight against the COVID-19 pandemic. Basic research advances in biotechnology and genetic engineering have already provided excellent progress and groundbreaking new discoveries in the field of the coronavirus biology and its epidemiology. In particular, for the vaccine development the advances in characterization of a capsid structure and identification of its antigens that can become targets for new vaccines. The development of the experimental vaccines requires a plethora of molecular techniques as well as strict compliance with safety procedures. The research and clinical data integrity, cross-validation of the results, and appropriated studies from the perspective of efficacy and potently side effects have recently become a hotly discussed topic. In this review, we present an update on latest advances and progress in an ongoing race to develop 52 different vaccines against SARS-CoV-2. Our analysis is focused on registered clinical trials (current as of November 04, 2020) that fulfill the international safety and efficacy criteria in the vaccine development. The requirements as well as benefits and risks of diverse types of SARS-CoV-2 vaccines are discussed including those containing whole-virus and live-attenuated vaccines, subunit vaccines, mRNA vaccines, DNA vaccines, live vector vaccines, and also plant-based vaccine formulation containing coronavirus-like particle (VLP). The challenges associated with the vaccine development as well as its distribution, safety and long-term effectiveness have also been highlighted and discussed.

Kelly, J. A., et al. (2020). "Structural and functional conservation of the programmed -1 ribosomal frameshift signal of SARS-CoV-2." bioRxiv.

17 years after the SARS-CoV epidemic, the world is facing the COVID-19 pandemic. COVID-19 is caused by a coronavirus named SARS-CoV-2. Given the most optimistic projections estimating that it will

take over a year to develop a vaccine, the best short-term strategy may lie in identifying virus-specific targets for small molecule interventions. All coronaviruses utilize a molecular mechanism called -1 PRF to control the relative expression of their proteins. Prior analyses of SARS-CoV revealed that it employs a structurally unique three-stemmed mRNA pseudoknot to stimulate high rates of -1 PRF, and that it also harbors a -1 PRF attenuation element. Altering -1 PRF activity negatively impacts virus replication, suggesting that this molecular mechanism may be therapeutically targeted. Here we present a comparative analysis of the original SARS-CoV and SARS-CoV-2 frameshift signals. Structural and functional analyses revealed that both elements promote similar rates of -1 PRF and that silent coding mutations in the slippery sites and in all three stems of the pseudoknot strongly ablated -1 PRF activity. The upstream attenuator hairpin activity has also been functionally retained. Small-angle x-ray scattering indicated that the pseudoknots in SARS-CoV and SARS-CoV-2 had the same conformation. Finally, a small molecule previously shown to bind the SARS-CoV pseudoknot and inhibit -1 PRF was similarly effective against -1 PRF in SARS-CoV-2, suggesting that such frameshift inhibitors may provide promising lead compounds to counter the current pandemic.

Kelly, J. A., et al. (2020). "Structural and functional conservation of the programmed -1 ribosomal frameshift signal of SARS coronavirus 2 (SARS-CoV-2)." J Biol Chem **295**(31): 10741-10748.

Approximately 17 years after the severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic, the world is currently facing the COVID-19 pandemic caused by SARS corona virus 2 (SARS-CoV-2). According to the most optimistic projections, it will take more than a year to develop a vaccine, so the best short-term strategy may lie in identifying virus-specific targets for small molecule-based interventions. All coronaviruses utilize a molecular mechanism called programmed -1 ribosomal frameshift (-1 PRF) to control the relative expression of their proteins. Previous analyses of SARS-CoV have revealed that it employs a structurally unique three-stemmed mRNA pseudoknot that stimulates high -1 PRF rates and that it also harbors a -1 PRF attenuation element. Altering -1 PRF activity impairs virus replication, suggesting that this activity may be therapeutically targeted. Here, we comparatively analyzed the SARS-CoV and SARS-CoV-2 frameshift signals. Structural and functional analyses revealed that both elements promote similar -1 PRF rates and that silent coding mutations in the slippery sites and in all three stems of the pseudoknot strongly ablate -1 PRF activity. We noted that the upstream attenuator hairpin activity is also functionally retained in both viruses, despite differences in the primary sequence in this region. Small-angle X-ray scattering analyses indicated that the pseudoknots in SARS-CoV and SARS-CoV-2 have the same conformation. Finally, a small molecule previously shown to bind the SARS-CoV pseudoknot and inhibit -1 PRF was similarly effective against -1 PRF in SARS-CoV-2, suggesting that such frameshift inhibitors may be promising lead compounds to combat the current COVID-19 pandemic.

Ketas, T. J., et al. (2021). "Antibody responses to SARS-CoV-2 mRNA vaccines are detectable in saliva." bioRxiv.

Vaccines are critical for curtailing the COVID-19 pandemic (1, 2). In the USA, two highly protective mRNA vaccines are available: BNT162b2 from Pfizer/BioNTech and mRNA-1273 from Moderna (3, 4). These vaccines induce antibodies to the SARS-CoV-2 S-protein, including neutralizing antibodies (NAbs) predominantly directed against the Receptor Binding Domain (RBD) (1-4). Serum NAbs are induced at modest levels within approximately 1 week of the first dose, but their titers are strongly boosted by a second dose at 3 (BNT162b2) or 4 weeks (mRNA-1273) (3, 4). SARS-CoV-2 is most commonly transmitted nasally or orally and infects cells in the mucosae of the respiratory and to some extent also the gastrointestinal tract (5). Although serum NAbs may be a correlate of protection against COVID-19, mucosal antibodies might directly prevent or limit virus acquisition by the nasal, oral and conjunctival routes (5). Whether the mRNA vaccines induce mucosal immunity has not been studied. Here, we report that antibodies to the S-protein and its RBD are present in saliva samples from mRNA-vaccinated healthcare workers (HCW). Within 1-2 weeks after their second dose, 37/37 and 8/8 recipients of the Pfizer and Moderna vaccines, respectively, had S-protein IgG antibodies in their saliva, while IgA was detected in a substantial proportion. These observations may be relevant to vaccine-mediated protection from SARS-CoV-2 infection and disease.

Khan, I., et al. (2020). "The Potential Vaccine Component for COVID-19: A Comprehensive Review of Global Vaccine Development Efforts." Cureus **12**(6): e8871.

The whole world is concerned about the pandemic of coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), due to fatality of this condition. This has become a public health emergency of international concern. No specific vaccine and medicine have proven effective in large-sized trials at this time. With the rapidly increasing number of positive cases and deaths, there is a dire need for effective treatments and an

effective vaccine for prevention. An urgent unmet need led to the planning and opening of multiple drug development trials for treatment and vaccine development. In this article, we have summarized data on cell receptor interactions and data on prospects of new vaccines targeting the deoxyribonucleic acid (DNA), messenger ribonucleic acid (mRNA), and viral minigenes. We have tabulated the available data on various clinical trials testing various aspects of COVID-19 vaccines.

Khan, K., et al. (2020). "COVID-19: A Review of Emerging Preventative Vaccines and Treatment Strategies." Cureus **12**(5): e8206.

COVID-19, which was first detected in the Hubei province of China, has become a global phenomenon. The effects and devastation on both health and economy have been global. At present, there is a substantial amount of research being done to discover suitable treatment modalities. Efforts have been made on the development of potential efficacious vaccines. The development of a vaccine can be complex, expensive as well as time-consuming. Currently, various ongoing clinical trials are in progress that are investigating either pharmacologic therapies or vaccines against this virus. We, in this brief review have tried to address the process and current development efforts of vaccine in progress.

Khurana, A., et al. (2021). "Role of nanotechnology behind the success of mRNA vaccines for COVID-19." Nano Today **38**: 101142.

The emergency use authorization (EUA) by the US-FDA for two mRNA-based vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) has brought hope of addressing the COVID-19 pandemic which has killed more than two million people globally. Nanotechnology has played a significant role in the success of these vaccines. Nanoparticles (NPs) aid in improving stability by protecting the encapsulated mRNA from ribonucleases and facilitate delivery of intact mRNA to the target site. The overwhelming success of these two mRNA based vaccines with ~95% efficacy in phase III clinical trials can be attributed to their unique nanocarrier, the "lipid nanoparticles" (LNPs). LNPs are unique compared with bilayered liposomes and provide improved stability of the cargo, possess rigid morphology, and aid in better cellular penetration. This EUA is a major milestone and showcases the immense potential of nanotechnology for vaccine delivery and for fighting against future pandemics. Currently, these two vaccines are aiding in the alleviation of the COVID-19 health crisis and demonstrate the potential utility of nanomedicine for tackling health problems at the global level.

Kim, J., et al. (2021). "Self-assembled mRNA vaccines." Adv Drug Deliv Rev **170**: 83-112.

mRNA vaccines have evolved from being a mere curiosity to emerging as COVID-19 vaccine front-runners. Recent advancements in the field of RNA technology, vaccinology, and nanotechnology have generated interest in delivering safe and effective mRNA therapeutics. In this review, we discuss design and self-assembly of mRNA vaccines. Self-assembly, a spontaneous organization of individual molecules, allows for design of nanoparticles with customizable properties. We highlight the materials commonly utilized to deliver mRNA, their physicochemical characteristics, and other relevant considerations, such as mRNA optimization, routes of administration, cellular fate, and immune activation, that are important for successful mRNA vaccination. We also examine the COVID-19 mRNA vaccines currently in clinical trials. mRNA vaccines are ready for the clinic, showing tremendous promise in the COVID-19 vaccine race, and have pushed the boundaries of gene therapy.

Kim, S. H., et al. (2021). "Adverse Events in Healthcare Workers after the First Dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 Vaccination: a Single Center Experience." J Korean Med Sci **36**(14): e107.

Coronavirus disease 2019 vaccinations for healthcare workers (HCWs) have begun in South Korea. To investigate adverse events (AEs) of the first dose of each vaccine, any symptom was collected daily for seven days after vaccination in a tertiary hospital. We found that 1,301 of 1,403 ChAdOx1 nCoV-19 recipients and 38 of 80 BNT162b2 recipients reported AEs respectively (90.9% vs. 52.5%): injection-site pain (77.7% vs. 51.2%), myalgia (60.5% vs. 11.2%), fatigue (50.7% vs. 7.5%), headache (47.4% vs. 7.5%), and fever (36.1% vs. 5%; $P < 0.001$ for all). Young HCWs reported more AEs with ChAdOx1 nCoV-19 than with BNT162b2. No incidences of anaphylaxis were observed. Only one serious AE required hospitalization for serious vomiting, and completely recovered. In conclusion, reported AEs were more common in recipients with ChAdOx1 nCoV-19 than in those with BNT162b2. However, most of the reported AEs were mild to moderate in severity. Sufficient explanation and preparation for expected AEs required to promote widespread vaccination.

Kis, Z., et al. (2020). "Resources, Production Scales and Time Required for Producing RNA Vaccines for the Global Pandemic Demand." Vaccines (Basel) **9**(1).

To overcome pandemics, such as COVID-19, vaccines are urgently needed at very high volumes. Here we assess the techno-economic feasibility of

producing RNA vaccines for the demand associated with a global vaccination campaign. Production process performance is assessed for three messenger RNA (mRNA) and one self-amplifying RNA (saRNA) vaccines, all currently under clinical development, as well as for a hypothetical next-generation saRNA vaccine. The impact of key process design and operation uncertainties on the performance of the production process was assessed. The RNA vaccine drug substance (DS) production rates, volumes and costs are mostly impacted by the RNA amount per vaccine dose and to a lesser extent by the scale and titre in the production process. The resources, production scale and speed required to meet global demand vary substantially in function of the RNA amount per dose. For lower dose saRNA vaccines, global demand can be met using a production process at a scale of below 10 L bioreactor working volume. Consequently, these small-scale processes require a low amount of resources to set up and operate. RNA DS production can be faster than fill-to-finish into multidose vials; hence the latter may constitute a bottleneck.

Klimek, L., et al. (2021). "Practical handling of allergic reactions to COVID-19 vaccines: A position paper from German and Austrian Allergy Societies AeDA, DGAKI, GPA and OGAI." Allergo J Int: 1-17.

Background: For the preventive treatment of the 2019 coronavirus disease (COVID-19) an unprecedented global research effort studied the safety and efficacy of new vaccine platforms that have not been previously used in humans. Less than one year after the discovery of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral sequence, these vaccines were approved for use in the European Union (EU) as well as in numerous other countries and mass vaccination efforts began. The so far in the EU approved mRNA vaccines BNT162b2 and mRNA-1273 are based on similar lipid-based nanoparticle carrier technologies; however, the lipid components differ. Severe allergic reactions and anaphylaxis after COVID-19 vaccination are very rare adverse events but have drawn attention due to potentially lethal outcomes and have triggered a high degree of uncertainty. Methods: Current knowledge on anaphylactic reactions to vaccines and specifically the new mRNA COVID-19 vaccines was compiled using a literature search in Medline, PubMed, as well as the national and international study and guideline registries, the Cochrane Library, and the Internet, with special reference to official websites of the World Health Organization (WHO), US Centers for Disease Control and Prevention (CDC), Robert Koch Institute (RKI), and Paul Ehrlich Institute (PEI). Results: Based on the international literature and previous experience, recommendations for prophylaxis, diagnosis and therapy of these allergic reactions are given by a panel of experts. Conclusion: Allergy testing is not necessary for the vast majority of allergic patients prior to COVID-19 vaccination with currently licensed vaccines. In case of allergic/anaphylactic reactions after vaccination, allergy workup is recommended, as it is for a small potential risk population prior to the first vaccination. Evaluation and approval of diagnostic tests should be done for this purpose.

Klimek, L., et al. (2021). Laryngorhinootologie **100**(5): 344-354.

Allergic reactions against mRNA COVID-19 vaccine are yet uncommon, but due to the high number of people who get this vaccination anaphylaxis will be seen. This is especially so in people who are sensitized to components of the vaccine. This article focuses on practical aspects of diagnostic possibilities, prevention, recognition and therapy of anaphylactic reactions. High-risk population, who should not get vaccinated; as well as people who need allergy diagnostics before vaccinations are discussed. In opinion of allergy experts patients with atopic allergies or venom allergies do not have a higher risk regarding anaphylaxic reaction due to COVID vaccination.

Klimek, L., et al. (2021). "[Allergic reactions to COVID-19 vaccines: evidence and practice-oriented approach]." Internist (Berl) **62**(3): 326-332.

Less than a year after the first detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), vaccines have been approved for routine use in numerous countries and have already been used in mass vaccination programs. Vaccines include the mRNA BNT162b2 and mRNA 1273. Allergic reactions and anaphylaxis account for a substantial proportion of the adverse reactions to these vaccines observed to date, but overall they are rare. The incidence of anaphylaxis in the context of SARS-CoV2 vaccination with the mRNA vaccines appears to be approximately 10-fold higher than with previous vaccines, at approximately 1 per 100,000 vaccine injections. One focus of the present article is a systematic review of the components of mRNA vaccines against " coronavirus disease 2019 " (COVID-19). Differences from established vaccines are addressed and the allergic potential of liposomes, polyethylene glycol, tromethamine/trometamol, and mRNA are discussed. Another focus is on the clinical presentation and course of allergic reactions to the COVID-19 vaccines. This is followed by a discussion of the therapeutic approach to anaphylactic reactions, as well as the drugs and medical supplies required to treat them. It is important to note that any vaccinee may be affected by anaphylaxis, regardless of whether or not allergic diseases are already known. Therefore,

every vaccination site and every vaccinator must be prepared to recognize and treat severe allergic reactions.

Klimek, L., et al. (2021). "Allergenic components of the mRNA-1273 vaccine for COVID-19: possible involvement of polyethylene glycol and IgG-mediated complement activation." Allergy.

Following the emergency use authorization of the mRNA-1273 vaccine on the 18(th) of December2020,two mRNAvaccinesare in current use for the prevention of coronavirus disease 2019 (COVID-19). For both mRNA vaccines, the phase IIIpivotal trials excluded individuals with a history of allergy tovaccine components.Immediately after the initiation of vaccination in the United Kingdom, Canada, and the US, anaphylactic reactions were reported. While the culprit trigger requires investigation, initial reports suggested the excipient polyethylene glycol 2000 (PEG-2000) -contained in both vaccines as the PEG-micellar carrier system - as the potentialculprit. Surface PEG chains form a hydrate shell to increasestability and prevent opsonization. Allergic reactions to such PEGylated lipids can be IgE-mediated,but may alsoresult from complement activation-related pseudoallergy (CARPA) that has been described insimilar liposomes. In addition, mRNA-1273 also contains tromethamine (trometamol), which has been reported to cause anaphylaxis to substances such asgadolinium-based contrast media. Skin prick, intradermal and epicutaneoustests, in vitro sIgE assessment, evaluation ofsIgG/IgM,as well as basophil activation tests are being used to demonstrate allergic reactions to various components of the vaccines.

Klimek, L., et al. (2021). "Severe allergic reactions after COVID-19 vaccination with the Pfizer/BioNTech vaccine in Great Britain and USA: Position statement of the German Allergy Societies: Medical Association of German Allergologists (AeDA), German Society for Allergology and Clinical Immunology (DGAKI) and Society for Pediatric Allergology and Environmental Medicine (GPA)." Allergo J Int **30**(2): 51-55.

Two employees of the National Health Service (NHS) in England developed severe allergic reactions following administration of BNT162b2 vaccine against COVID-19 (coronavirus disease 2019). The British SmPC for the BNT162b2 vaccine already includes reference to a contraindication for use in individuals who have had an allergic reaction to the vaccine or any of its components. As a precautionary measure, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued interim guidance to the NHS not to vaccinate in principle in "patients with severe allergies". Allergic reactions to vaccines are very rare, but vaccine components are known to cause allergic reactions. BNT162b2 is a vaccine based on an mRNA embedded in lipid nanoparticles and blended with other substances to enable its transport into the cells. In the pivotal phase III clinical trial, the BNT162b2 vaccine was generally well tolerated, but this large clinical trial, used to support vaccine approval by the MHRA and US Food and Drug Administration, excluded individuals with a "history of a severe adverse reaction related to the vaccine and/or a severe allergic reaction (e.g., anaphylaxis) to a component of the study medication". Vaccines are recognized as one of the most effective public health interventions. This repeated administration of a foreign protein (antigen) necessitates a careful allergological history before each application and diagnostic clarification and a risk-benefit assessment before each injection. Severe allergic reactions to vaccines are rare but can be life-threatening, and it is prudent to raise awareness of this hazard among vaccination teams and to take adequate precautions while more experience is gained with this new vaccine.

Knezevic, I., et al. (2021). "Development of mRNA Vaccines: Scientific and Regulatory Issues." Vaccines (Basel) **9**(2).

The global research and development of mRNA vaccines have been prodigious over the past decade, and the work in this field has been stimulated by the urgent need for rapid development of vaccines in response to an emergent disease such as the current COVID-19 pandemic. Nevertheless, there remain gaps in our understanding of the mechanism of action of mRNA vaccines, as well as their long-term performance in areas such as safety and efficacy. This paper reviews the technologies and processes used for developing mRNA prophylactic vaccines, the current status of vaccine development, and discusses the immune responses induced by mRNA vaccines. It also discusses important issues with regard to the evaluation of mRNA vaccines from regulatory perspectives. Setting global norms and standards for biologicals including vaccines to assure their quality, safety and efficacy has been a WHO mandate and a core function for more than 70 years. New initiatives are ongoing at WHO to arrive at a broad consensus to formulate international guidance on the manufacture and quality control, as well as nonclinical and clinical evaluation of mRNA vaccines, which is deemed necessary to facilitate international convergence of manufacturing and regulatory practices and provide support to National Regulatory Authorities in WHO member states.

Korth, J., et al. (2021). "Impaired Humoral Response in Renal Transplant Recipients to SARS-CoV-2 Vaccination with BNT162b2 (Pfizer-BioNTech)."

Viruses **13**(5).

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has a major impact on transplant recipients, with mortality rates up to 20%. Therefore, the effect of established messenger RNA (mRNA)-based SARS-CoV-2 vaccines have to be evaluated for solid organ transplant patients (SOT) since they are known to have poor responses after vaccination. We investigated the SARS-CoV-2 immune response via SARS-CoV-2 IgG detection in 23 renal transplant recipients after two doses of the mRNA-based SARS-CoV-2 vaccine BNT162b2 following the standard protocol. The antibody response was evaluated once with an anti-SARS-CoV-2 IgG CLIA 15.8 +/- 3.0 days after the second dose. As a control, SARS-CoV-2 IgG was determined in 23 healthcare workers (HCW) and compared to the patient cohort. Only 5 of 23 (22%) renal transplant recipients were tested positive for SARS-CoV-2 IgG antibodies after the second dose of vaccine. In contrast, all 23 (100%) HCWs were tested positive for antibodies after the second dose. Thus, the humoral response of renal transplant recipients after two doses of the mRNA-based vaccine BNT162b2 (Pfizer-BioNTech, Kronach, Germany) is impaired and significantly lower compared to healthy controls (22% vs. 100%; p = 0.0001). Individual vaccination strategies might be beneficial in these vulnerable patients.

Kounis, N. G., et al. (2021). "Allergic Reactions to Current Available COVID-19 Vaccinations: Pathophysiology, Causality, and Therapeutic Considerations." Vaccines (Basel) **9**(3).

Vaccines constitute the most effective medications in public health as they control and prevent the spread of infectious diseases and reduce mortality. Similar to other medications, allergic reactions can occur during vaccination. While most reactions are neither frequent nor serious, anaphylactic reactions are potentially life-threatening allergic reactions that are encountered rarely, but can cause serious complications. The allergic responses caused by vaccines can stem from activation of mast cells via Fcepsilon receptor-1 type I reaction, mediated by the interaction between immunoglobulin E (IgE) antibodies against a particular vaccine, and occur within minutes or up to four hours. The type IV allergic reactions initiate 48 h after vaccination and demonstrate their peak between 72 and 96 h. Non-IgE-mediated mast cell degranulation via activation of the complement system and via activation of the Mas-related G protein-coupled receptor X2 can also induce allergic reactions. Reactions are more often caused by inert substances, called excipients, which are added to vaccines to improve stability and absorption, increase solubility, influence palatability, or create a distinctive appearance, and not by the active vaccine itself. Polyethylene glycol, also known as macrogol, in the currently available Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines, and polysorbate 80, also known as Tween 80, in AstraZeneca and Johnson & Johnson COVID-19 vaccines, are excipients mostly incriminated for allergic reactions. This review will summarize the current state of knowledge of immediate and delayed allergic reactions in the currently available vaccines against COVID-19, together with the general and specific therapeutic considerations. These considerations include: The incidence of allergic reactions and deaths under investigation with the available vaccines, application of vaccination in patients with mast cell disease, patients who developed an allergy during the first dose, vasovagal symptoms masquerading as allergic reactions, the COVID-19 vaccination in pregnancy, deaths associated with COVID-19 vaccination, and questions arising in managing of this current ordeal. Careful vaccine-safety surveillance over time, in conjunction with the elucidation of mechanisms of adverse events across different COVID-19 vaccine platforms, will contribute to the development of a safe vaccine strategy. Allergists' expertise in proper diagnosis and treatment of allergic reactions is vital for the screening of high-risk individuals.

Kronbichler, A., et al. (2021). "Recommendations for the use of COVID-19 vaccines in patients with immune-mediated kidney diseases." Nephrol Dial Transplant.

Coronavirus Disease 19 (COVID-19) vaccine platforms are becoming available and are the most promising strategy to curb the spread of SARS-CoV-2 infections. However, numerous uncertainties exist regarding the pros and cons of vaccination, especially in patients with (immune-mediated) kidney diseases on immunosuppressive drugs. Here, members of the Immunonephrology Working Group (IWG) of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) discuss thirteen frequently-asked questions regarding safety and efficacy of the most promising vaccine candidates. Post-marketing surveillance should be performed to estimate the rate of vaccine response (humoral and cellular) of different vaccine platforms, and surveillance of disease activity following administration of COVID-19 vaccines. Some of the candidates induce signaling pathways which also promote autoimmune kidney diseases, e.g. type I interferons in systemic lupus erythematosus. Efficacy estimates would thus far favor the use of selected COVID-19 vaccines, such as BNT162b2, mRNA-1273 or Gam-COVID-Vac. Humoral immune response after vaccination should be monitored using appropriate

assays. Even in the absence of neutralizing antibodies patients might be protected by a sufficient cellular immune response capable to reduce severity of COVID-19. A reduced vaccine response after the use of CD20-depleting agents is anticipated, and it is particularly important to discuss strategies to improve vaccine response with these patients. Distancing and shielding measures remain important as not all vaccines fully protect from coronavirus infection. In-depth information about the most pressing vaccine questions is essential to reduce vaccine hesitancy of patients.

Kuder, M. M., et al. (2021). "Anaphylaxis to vaccinations: A review of the literature and evaluation of the COVID-19 mRNA vaccinations." Cleve Clin J Med.

Recent reports of allergic reactions to the Pfizer-BioNTech and the Moderna COVID-19 vaccines have resulted in questions about how and to whom they can be safely administered. Although anaphylaxis was not observed in clinical trials for either vaccine, there have been 21 reported possible cases of anaphylaxis associated with the Pfizer vaccine (11.1 cases per million doses administered) and 10 possible cases associated with the Moderna vaccine (2.5 anaphylaxis cases per million doses administered). The etiology of anaphylaxis in these cases is not fully understood and is an area of active research. The overall incidence of anaphylaxis to COVID-19 mRNA vaccines is very low. By following recommendations from the US Centers for Disease Control and Prevention, an overwhelming majority of the US population can be safely immunized.

Kuderer, N. M., et al. (2021). "Challenges and Opportunities for COVID-19 Vaccines in Patients with Cancer." Cancer Invest **39**(3): 205-213.

Given the rapidly expanding global spread of the SARS-Co-V-2 virus and the expanding number of individuals with the serious and potentially fatal illness, COVID-19, there is an urgent need for safe and effective vaccines. Based on compelling evidence that patients with cancer are at increased risk for greater morbidity and mortality with COVID-19, several professional organizations have provided early guidance on the role of COVID-19 vaccines in patients with malignant disease. In this commentary we review the available data on the efficacy and safety of the approved and forthcoming vaccines in patients with cancer. Based on a review of the totality of available evidence, we recommend that most patients with cancer should receive the recommended dose and schedule of one of the COVID-19 vaccines when available. We encourage industry, regulators and professional research organizations to carefully track the efficacy and safety of COVID-19 vaccination in patients with cancer in the real world setting and routinely report unanticipated adverse events and signs of loss of efficacy. Particular attention is needed for patients on active cancer therapy to carefully evaluate efficacy and safety in relationship to the timing of vaccination relative to that of active cancer treatment and immunosuppression.

Kulikowski, C. A. (2021). "Pandemics: Historically Slow "Learning Curve" Leading to Biomedical Informatics and Vaccine Breakthroughs." Yearb Med Inform.

BACKGROUND: The worldwide tragedy of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic vividly demonstrates just how inadequate mitigation and control of the spread of infectious diseases can be when faced with a new microorganism with unknown pathogenic effects. Responses by governments in charge of public health, and all other involved organizations, have proved largely wanting. Data infrastructure and the information and communication systems needed to deal with the pandemic have likewise not been up to the task. Nevertheless, after a year of the worldwide outbreak, hope arises from this being the first major pandemic event in history where genomic and related biosciences - relying on biomedical informatics - have been essential in decoding the viral sequence data and producing the mRNA and other biotechnologies that unexpectedly rapidly have led to investigation, design, development, and testing of useful vaccines. Medical informatics may also help support public health actions and clinical interventions - but scalability and impact will depend on overcoming ingrained human shortcomings to deal with complex socio-economic, political, and technological disruptions together with the many ethical challenges presented by pandemics. OBJECTIVES: The principal goal is to review the history of biomedical information and healthcare practices related to past pandemics in order to illustrate just how exceptional and dependent on biomedical informatics are the recent scientific insights into human immune responses to viral infection, which are enabling rapid antiviral vaccine development and clinical management of severe cases - despite the many societal challenges ahead. METHODS: This paper briefly reviews some of the key historical antecedents leading up to modern insights into epidemic and pandemic processes with their biomedical and healthcare information intended to guide practitioners, agencies, and the lay public in today's ongoing pandemic events. CONCLUSIONS: Poor scientific understanding and excessively slow learning about infectious disease processes and mitigating behaviors have stymied effective treatment until the present time. Advances in insights about immune systems, genomes,

proteomes, and all the other -omes, became a reality thanks to the key sequencing technologies and biomedical informatics that enabled the Human Genome Project, and only now, 20 years later, are having an impact in ameliorating devastating zoonotic infectious pandemics, including the present SARS-CoV-2 event through unprecedently rapid vaccine development. In the future these advances will hopefully also enable more targeted prevention and treatment of disease. However, past and present shortcomings of most of the COVID-19 pandemic responses illustrate just how difficult it is to persuade enough people - and especially political leaders - to adopt societally beneficial risk-avoidance behaviors and policies, even as these become better understood.

Kumar, V., et al. (2020). "Withanone and Withaferin-A are predicted to interact with transmembrane protease serine 2 (TMPRSS2) and block entry of SARS-CoV-2 into cells." J Biomol Struct Dyn: 1-13.

Coronavirus disease 2019 (COVID-19) initiated in December 2019 in Wuhan, China and became pandemic causing high fatality and disrupted normal life calling world almost to a halt. Causative agent is a novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2/2019-nCoV). While new line of drug/vaccine development has been initiated world-wide, in the current scenario of high infected numbers, severity of the disease and high morbidity, repurposing of the existing drugs is heavily explored. Here, we used a homology-based structural model of transmembrane protease serine 2 (TMPRSS2), a cell surface receptor, required for entry of virus to the target host cell. Using the strengths of molecular docking and molecular dynamics simulations, we examined the binding potential of Withaferin-A (Wi-A), Withanone (Wi-N) and caffeic acid phenethyl ester to TPMRSS2 in comparison to its known inhibitor, Camostat mesylate. We found that both Wi-A and Wi-N could bind and stably interact at the catalytic site of TMPRSS2. Wi-N showed stronger interactions with TMPRSS2 catalytic residues than Wi-A and was also able to induce changes in its allosteric site. Furthermore, we investigated the effect of Wi-N on TMPRSS2 expression in MCF7 cells and found remarkable downregulation of TMPRSS2 mRNA in treated cells predicting dual action of Wi-N to block SARS-CoV-2 entry into the host cells. Since the natural compounds are easily available/affordable, they may even offer a timely therapeutic/preventive value for the management of SARS-CoV-2 pandemic. We also report that Wi-A/Wi-N content varies in different parts of Ashwagandha and warrants careful attention for their use.Communicated by Ramaswamy H. Sarma.

Kwong, P. D., et al. (2020). "Antibody-guided structure-based vaccines." Semin Immunol **50**: 101428.

The vaccine field is pursuing diverse approaches to translate the molecular insights from analyses of effective antibodies and their targeted epitopes into immunogens capable of eliciting protective immune responses. Here we review current antibody-guided strategies including conformation-based, epitope-based, and lineage-based vaccine approaches, which are yielding promising vaccine candidates now being evaluated in clinical trials. We summarize directions being employed by the field, including the use of sequencing technologies to monitor and track developing immune responses for understanding and improving antibody-based immunity. We review opportunities and challenges to transform powerful new discoveries into safe and effective vaccines, which are encapsulated by vaccine efforts against a variety of pathogens including HIV-1, influenza A virus, malaria parasites, respiratory syncytial virus, and SARS-CoV-2. Overall, this review summarizes the extensive progress that has been made to realize antibody-guided structure-based vaccines, the considerable challenges faced, and the opportunities afforded by recently developed molecular approaches to vaccine development.

Lacson, E., et al. (2021). "Immunogenicity of SARS-CoV-2 Vaccine in Dialysis." medRxiv.

Background: Patients receiving maintenance dialysis represent a high risk, immune-compromised population with 15-25% COVID mortality rate who were unrepresented in clinical trials evaluated for mRNA vaccines' emergency use authorization. Method: All patients receiving maintenance dialysis that received two doses of SARS-CoV-2 mRNA vaccines with antibody test results drawn >/=14 days after the second dose, as documented in the electronic health record through March 18, 2021 were included. We report seroresponse based on levels of immunoglobulin-G against the receptor binding domain of the S1 subunit of SARS-CoV-2 spike antigen (seropositive >/=2) using FDA-approved semi-quantitative chemiluminescent assay (ADVIA Centaur(R) XP/XPT COV2G). Results: Among 186 dialysis patients from 32 clinics in 8 states tested 23+/-8 days after receiving 2 vaccine doses, mean age was 68+/-12 years, with 47% women, 21% Black, 26% residents in long-term care facilities and 97% undergoing in-center hemodialysis. Overall seropositive rate was 165/186 (88.7%) with 70% at maximum titer and with no significant difference in seropositivity between BNT162b2/Pfizer (N=148) and mRNA-1273/Moderna (N=18) vaccines (88.1% vs. 94.4%, p=0.42). Among patients with COVID-19 history, seropositive rate was 38/38 (100%) with 97%

at maximum titer. Conclusion: Most patients receiving maintenance dialysis were seropositive after two doses of BNT162b2/Pfizer or mRNA-1273/Moderna vaccine. Early evidence suggests that vaccinated dialysis patients with prior COVID-19 develop robust antibody response. These results support an equitable and aggressive vaccination strategy for eligible dialysis patients, regardless of age, sex, race, ethnicity, or disability, to prevent the extremely high morbidity and mortality associated with COVID-19 in this high risk population. Significance: In this retrospective observational evaluation of SARS-CoV-2 mRNA vaccine response defined by detectable levels of immunoglobulin-G against the receptor binding domain of the S1 subunit of SARS-CoV-2 spike antigen of >/=2 in serum of patients receiving maintenance dialysis, 165/186 (88.7%) were found to be seropositive (with 70% at maximum titer) at least 14 days after completing the second dose. No significant differences were observed by race or other subgroup or by vaccine manufacturer. Therefore, an equitable and aggressive vaccination strategy for all eligible maintenance dialysis patients, regardless of age, sex, race, ethnicity, or disability, is warranted to prevent the extremely high morbidity and mortality associated with COVID-19 in this high risk population.

Laczko, D., et al. (2020). "A Single Immunization with Nucleoside-Modified mRNA Vaccines Elicits Strong Cellular and Humoral Immune Responses against SARS-CoV-2 in Mice." Immunity **53**(4): 724-732 e727.

SARS-CoV-2 infection has emerged as a serious global pandemic. Because of the high transmissibility of the virus and the high rate of morbidity and mortality associated with COVID-19, developing effective and safe vaccines is a top research priority. Here, we provide a detailed evaluation of the immunogenicity of lipid nanoparticle-encapsulated, nucleoside-modified mRNA (mRNA-LNP) vaccines encoding the full-length SARS-CoV-2 spike protein or the spike receptor binding domain in mice. We demonstrate that a single dose of these vaccines induces strong type 1 CD4(+) and CD8(+) T cell responses, as well as long-lived plasma and memory B cell responses. Additionally, we detect robust and sustained neutralizing antibody responses and the antibodies elicited by nucleoside-modified mRNA vaccines do not show antibody-dependent enhancement of infection in vitro. Our findings suggest that the nucleoside-modified mRNA-LNP vaccine platform can induce robust immune responses and is a promising candidate to combat COVID-19.

Lamb, Y. N. (2021). "BNT162b2 mRNA COVID-19 Vaccine: First Approval." Drugs **81**(4): 495-501.

BNT162b2 (Comirnaty((R)); BioNTech and Pfizer) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine for the prevention of the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. BNT162b2 encodes the SARS-CoV-2 spike protein, the expression of which elicits immune responses against the antigen in recipients. In early December 2020, BNT162b2 received a temporary emergency use authorization (EUA) in the UK and, subsequently, a series of approvals or authorizations for emergency use in Bahrain, Canada, Mexico, Saudi Arabia and the USA. Soon after, BNT162b2 received conditional marketing authorizations in Switzerland (19 December 2020) and the EU (21 December 2020) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. BNT162b2 is administered intramuscularly in a two-dose regimen. This article summarizes the milestones in the development of BNT162b2 leading to these first approvals for the prevention of COVID-19.

Leach, S. (2020). "[At least 68 vaccine candidates under development]." Lakartidningen **117**.

The development of vaccines against SARS-CoV-2 is progressing at an unparalleled speed. As of the 29th of March, there were at least 68 vaccine candidates comprising several different vaccine designs, including whole killed virus, subunit, attenuated, viral vector, DNA and mRNA vaccines. Whilst it usually takes 10-15 years to develop a vaccine, it has only taken just over 9 weeks from the publication of the viral genetic sequence for the first vaccine candidate to reach clinical testing. Development has been expediated by using existing technological platforms and by performing preclinical and clinical testing simultaneously.

Lederer, K., et al. (2020). "SARS-CoV-2 mRNA Vaccines Foster Potent Antigen-Specific Germinal Center Responses Associated with Neutralizing Antibody Generation." Immunity **53**(6): 1281-1295 e1285.

The deployment of effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical to eradicate the coronavirus disease 2019 (COVID-19) pandemic. Many licensed vaccines confer protection by inducing long-lived plasma cells (LLPCs) and memory B cells (MBCs), cell types canonically generated during germinal center (GC) reactions. Here, we directly compared two vaccine platforms-mRNA vaccines and a recombinant protein formulated with an MF59-like adjuvant-looking for their abilities to quantitatively and qualitatively shape SARS-CoV-2-specific primary GC responses over time. We demonstrated that a single immunization

with SARS-CoV-2 mRNA, but not with the recombinant protein vaccine, elicited potent SARS-CoV-2-specific GC B and T follicular helper (Tfh) cell responses as well as LLPCs and MBCs. Importantly, GC responses strongly correlated with neutralizing antibody production. mRNA vaccines more efficiently induced key regulators of the Tfh cell program and influenced the functional properties of Tfh cells. Overall, this study identifies SARS-CoV-2 mRNA vaccines as strong candidates for promoting robust GC-derived immune responses.

Lee, H., et al. (2021). "Do Corticosteroid Injections for the Treatment of Pain Influence the Efficacy of mRNA COVID-19 Vaccines?" Pain Med **22**(4): 994-1000.

MYTH: Corticosteroid injection for the treatment of pain and inflammation is known to decrease the efficacy of the messenger ribonucleic acid (mRNA) vaccines for coronavirus disease 2019 (COVID-19). FACT: There is currently no direct evidence to suggest that a corticosteroid injection before or after the administration of an mRNA COVID-19 vaccine decreases the efficacy of the vaccine.However, based on the known timeline of hypothalamic-pituitary-adrenal (HPA) axis suppression following epidural and intraarticular corticosteroid injections, and the timeline of the reported peak efficacy of the Pfizer-BioNTech and Moderna vaccines, physicians should consider timing an elective corticosteroid injection such that it is administered no less than 2 weeks prior to a COVID-19 mRNA vaccine dose and no less than 1 week following a COVID-19 mRNA vaccine dose, whenever possible.

Li, J., et al. (2021). "Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study." Nat Med.

An effective vaccine is needed to end the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Here, we assess the preliminary safety, tolerability and immunogenicity data from an ongoing single-center (in Jiangsu province, China), parallel-group, double-blind phase 1 trial of the vaccine candidate BNT162b1 in 144 healthy SARS-CoV-2-naive Chinese participants. These participants are randomized 1:1:1 to receive prime and boost vaccinations of 10 microg or 30 microg BNT162b1 or placebo, given 21 d apart, with equal allocation of younger (aged 18-55 years) and older adults (aged 65-85 years) to each treatment group (ChiCTR2000034825). BNT162b1 encodes the SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) and is one of several messenger RNA-based vaccine candidates under clinical investigation. Local reactions and systemic events were generally dose dependent, transient and mild to moderate. Fever was the only grade 3 adverse event. BNT162b1 induced robust interferon-gamma T cell responses to a peptide pool including the RBD in both younger and older Chinese adults, and geometric mean neutralizing titers reached 2.1-fold (for younger participants) and 1.3-fold (for the older participants) that of a panel of COVID-19 convalescent human sera obtained at least 14 d after positive SARS-CoV-2 polymerase chain reaction test. In summary, BNT162b1 has an acceptable safety profile and produces high levels of humoral and T cell responses in an Asian population.

Liu, C. H., et al. (2021). "Highlight of severe acute respiratory syndrome coronavirus-2 vaccine development against COVID-19 pandemic." J Chin Med Assoc **84**(1): 9-13.

The pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has brought an unprecedented impact upon the global economy and public health. Although the SARS-CoV-2 virology has been gradually investigated, measures to combat this new threat in public health are still absent. To date, no certificated drug or vaccine has been developed for the treatment or prevention of coronavirus disease Extensive researches and international coordination has been conducted to rapidly develop novel vaccines against SARS-CoV-2 pandemic. Several major breakthroughs have been made through the identification of the genetic sequence and structural/non-structural proteins of SARS-CoV-2, which enabled the development of RNA-, DNA-based vaccines, subunit vaccines, and attenuated viral vaccines. In this review article, we present an overview of the recent advances of SARS-CoV-2 vaccines and the challenges that may be encountered in the development process, highlighting the advantages and disadvantages of these approaches that may help in effectively countering COVID-19.

Liu, R., et al. (2021). "MVA Vector Vaccines Inhibit SARS CoV-2 Replication in Upper and Lower Respiratory Tracts of Transgenic Mice and Prevent Lethal Disease." bioRxiv.

Replication-restricted modified vaccinia virus Ankara (MVA) is a licensed smallpox vaccine and numerous clinical studies investigating recombinant MVAs (rMVAs) as vectors for prevention of other infectious diseases have been completed or are in progress. Two rMVA COVID-19 vaccine trials are at an initial stage, though no animal protection studies have been reported. Here, we characterize rMVAs expressing the S protein of CoV-2. Modifications of full length S individually or in combination included two proline substitutions, mutations of the furin recognition site and deletion of the endoplasmic

retrieval signal. Another rMVA in which the receptor binding domain (RBD) flanked by the signal peptide and transmembrane domains of S was also constructed. Each modified S protein was displayed on the surface of rMVA-infected human cells and was recognized by anti-RBD antibody and by soluble hACE2 receptor. Intramuscular injection of mice with the rMVAs induced S-binding and pseudovirus-neutralizing antibodies. Boosting occurred following a second homologous rMVA but was higher with adjuvanted purified RBD protein. Weight loss and lethality following intranasal infection of transgenic hACE2 mice with CoV-2 was prevented by one or two immunizations with rMVAs or by passive transfer of serum from vaccinated mice. One or two rMVA vaccinations also prevented recovery of infectious CoV-2 from the lungs. A low amount of virus was detected in the nasal turbinates of only one of eight rMVA-vaccinated mice on day 2 and none later. Detection of subgenomic mRNA in turbinates on day 2 only indicated that replication was abortive in immunized animals. Significance: Vaccines are required to control COVID-19 during the pandemic and possibly afterwards. Recombinant nucleic acids, proteins and virus vectors that stimulate immune responses to the CoV-2 S protein have provided protection in experimental animal or human clinical trials, though questions remain regarding their ability to prevent spread and the duration of immunity. The present study focuses on replication-restricted modified vaccinia virus Ankara (MVA), which has been shown to be a safe, immunogenic and stable smallpox vaccine and a promising vaccine vector for other infectious diseases and cancer. In a transgenic mouse model, one or two injections of recombinant MVAs that express modified forms of S inhibited CoV-2 replication in the upper and lower respiratory tracts and prevented severe disease.

Lombardi, A., et al. (2021). "Mini Review Immunological Consequences of Immunization With COVID-19 mRNA Vaccines: Preliminary Results." Front Immunol **12**: 657711.

Background: BNT162b2 and mRNA-1273 are the two recently approved mRNA-based vaccines against COVID-19 which has shown excellent safety and efficacy. Preliminary data about specific and neutralizing antibodies is available covering the first 100 days after vaccination. Methods: We reviewed all the publications regarding the immunologic consequences of BNT162b2 and mRNA-1273 vaccination. A summary of specific antibodies concentration and neutralizing antibodies titers elicited by each vaccine is provided. Results: BNT162b2 and mRNA-1273 displayed a reassuring safety and efficacy profile, with the latter above 94%. They can elicit specific antibodies titers and neutralizing antibodies concentrations that are far superior from those observed among COVID-19 human convalescent serum, across a wide span of age, for at least 100 days after vaccination. Moreover, the vaccine-induced T cellular response is oriented toward a TH1 response and no evidence of vaccine-enhanced disease have been reported. Discussion: BNT162b2 and mRNA-1273 can elicit specific antibodies titers and neutralizing antibodies concentrations above those observed among COVID-19 human convalescent serum in the first 100 days after vaccination. Data about vaccine efficacy in those with previous COVID-19 or immunocompromised is still limited.

Loo, K. Y., et al. (2021). "COVID-19: Insights into Potential Vaccines." Microorganisms **9**(3).

People around the world ushered in the new year 2021 with a fear of COVID-19, as family members have lost their loved ones to the disease. Millions of people have been infected, and the livelihood of many has been jeopardized due to the pandemic. Pharmaceutical companies are racing against time to develop an effective vaccine to protect against COVID-19. Researchers have developed various types of candidate vaccines with the release of the genetic sequence of the SARS-CoV-2 virus in January. These include inactivated viral vaccines, protein subunit vaccines, mRNA vaccines, and recombinant viral vector vaccines. To date, several vaccines have been authorized for emergency use and they have been administered in countries across the globe. Meanwhile, there are also vaccine candidates in Phase III clinical trials awaiting results and approval from authorities. These candidates have shown positive results in the previous stages of the trials, whereby they could induce an immune response with minimal side effects in the participants. This review aims to discuss the different vaccine platforms and the clinical trials of the candidate vaccines.

Lozada-Requena, I. and C. Nunez Ponce (2020). Rev Peru Med Exp Salud Publica **37**(2): 312-319.

Disease caused by the new coronavirus (COVID-19) is characterized by fever, cough, and affection of the lower respiratory tract. It is associated with age, comorbidities and a weakened immune system. Typically, lymphopenias have been evidenced in severe cases and an excessive production of inflammatory cytokines (cytokine storm), which would explain the role of the hyperinflammatory response in the pathogenesis of COVID-19. Secondary inflammatory responses from virus reinfections may induce antibody-dependent enhancement (ADE), a viremic phenomenon that may be an alternative mechanism of cellular infection and should be

considered when designing vaccines or immunotherapies involving the stimulation of neutralizing antibodies or the use of monoclonal antibodies. Currently, no vaccines or treatments demonstrate safety and efficacy in patients with COVID-19. However, the results from phase III clinical trials which involve the application of an mRNA (messenger ribonucleic acid) nucleic acid vaccine and an antiviral drug (remdisivir), are yet to be concluded. For the time being, the best measure to prevent the spread of COVID-19 is by implementing social isolation, this measure has been adopted by several countries as recommended by the World Health Organization (WHO).

Malladi, S. K., et al. (2020). "Design of a highly thermotolerant, immunogenic SARS-CoV-2 spike fragment." J Biol Chem.

Virtually all SARS-CoV-2 vaccines currently in clinical testing are stored in a refrigerated or frozen state prior to use. This is a major impediment to deployment in resource-poor settings. Furthermore, several of them use viral vectors or mRNA. In contrast to protein subunit vaccines, there is limited manufacturing expertise for these nucleic acid-based modalities, especially in the developing world. Neutralizing antibodies, the clearest known correlate of protection against SARS-CoV-2, are primarily directed against the Receptor Binding Domain (RBD) of the viral spike protein, suggesting that a suitable RBD construct might serve as a more accessible vaccine ingredient. We describe a monomeric, glycan engineered RBD protein fragment that is expressed at a purified yield of 214 mg/L in unoptimized, mammalian cell culture and, in contrast to a stabilized spike ectodomain, is tolerant of exposure to temperatures as high as 100 degrees C when lyophilized, up to 70 degrees C in solution and stable for over four weeks at 37 degrees C. In prime:boost guinea pig immunizations, when formulated with the MF59-like adjuvant AddaVax, the RBD derivative elicited neutralizing antibodies with an endpoint geometric mean titer of ~415 against replicative virus, comparing favourably with several vaccine formulations currently in the clinic. These features of high yield, extreme thermotolerance and satisfactory immunogenicity suggest that such RBD subunit vaccine formulations hold great promise to combat COVID-19.

Mathioudakis, A. G., et al. (2021). "Self-Reported Real-World Safety and Reactogenicity of COVID-19 Vaccines: A Vaccine Recipient Survey." Life (Basel) **11**(3).

An online survey was conducted to compare the safety, tolerability and reactogenicity of available COVID-19 vaccines in different recipient groups. This survey was launched in February 2021 and ran for 11 days. Recipients of a first COVID-19 vaccine dose >/=7 days prior to survey completion were eligible. The incidence and severity of vaccination side effects were assessed. The survey was completed by 2002 respondents of whom 26.6% had a prior COVID-19 infection. A prior COVID-19 infection was associated with an increased risk of any side effect (risk ratio 1.08, 95% confidence intervals (1.05-1.11)), fever (2.24 (1.86-2.70)), breathlessness (2.05 (1.28-3.29)), flu-like illness (1.78 (1.51-2.10)), fatigue (1.34 (1.20-1.49)) and local reactions (1.10 (1.06-1.15)). It was also associated with an increased risk of severe side effects leading to hospital care (1.56 (1.14-2.12)). While mRNA vaccines were associated with a higher incidence of any side effect (1.06 (1.01-1.11)) compared with viral vector-based vaccines, these were generally milder ($p < 0.001$), mostly local reactions. Importantly, mRNA vaccine recipients reported a considerably lower incidence of systemic reactions (RR < 0.6) including anaphylaxis, swelling, flu-like illness, breathlessness and fatigue and of side effects requiring hospital care (0.42 (0.31-0.58)). Our study confirms the findings of recent randomised controlled trials (RCTs) demonstrating that COVID-19 vaccines are generally safe with limited severe side effects. For the first time, our study links prior COVID-19 illness with an increased incidence of vaccination side effects and demonstrates that mRNA vaccines cause milder, less frequent systemic side effects but more local reactions.

Mazzoni, A., et al. (2021). "First-dose mRNA vaccination is sufficient to reactivate immunological memory to SARS-CoV-2 in recovered COVID-19 subjects." J Clin Invest.

The characterization of the adaptive immune response to COVID-19 vaccination in individuals who recovered from SARS-CoV-2 infection may define current and future clinical practice. To determine the effect of two doses BNT162b2 mRNA COVID-19 vaccination schedule in individuals who recovered from COVID-19 (COVID-19 recovered) compared to naive subjects, we evaluated SARS-CoV-2 Spike-specific T and B cell responses, as well as specific IgA, IgG, IgM and neutralizing antibodies titers in 22 individuals who received BNT162b2 mRNA COVID-19 vaccine, 11 of which had a previous history of SARS-CoV-2 infection. Evaluations were performed before vaccination and then weekly until 7 days post second injection. Data obtained clearly showed that one vaccine dose is sufficient to increase both cellular and humoral immune response in COVID-19 recovered subjects without any additional improvement after the second dose. On the contrary, the second dose is proved mandatory in naive ones to further enhance the immune response. These findings were further

confirmed at serological level in a larger cohort of naive (68) and COVID-19 recovered (29) subjects, tested up to 50 days post vaccination. These results question whether a second vaccine injection in COVID-19 recovered subjects is required and indicate that millions of vaccine doses may be redirected to naive individuals, thus shortening the time to reach herd immunity.

McEllistrem, M. C., et al. (2021). "Single dose of a mRNA SARS-CoV-2 vaccine is associated with lower nasopharyngeal viral load among nursing home residents with asymptomatic COVID-19." Clin Infect Dis.

In nursing home residents with asymptomatic COVID-19 diagnosed through twice-weekly surveillance testing, single dose BNT162b2 vaccination (Pfizer-BioNTech) was associated with -2.4 mean log10 lower nasopharyngeal viral load than detected in absence of vaccination (p=0.004). Since viral load is linked to transmission, single dose mRNA SARS-CoV-2 vaccination may help control outbreaks.

McIntosh, L. J., et al. (2021). "COVID-19 Vaccination-Related Uptake on FDG PET/CT: An Emerging Dilemma and Suggestions for Management." AJR Am J Roentgenol.

As mass COVID-19 vaccination is underway, radiologists are encountering transient FDG uptake in normal or enlarged axillary, supraclavicular, and cervical lymph nodes after ipsilateral deltoid vaccination. This phenomenon may confound interpretation in oncology patients undergoing FDG PET/CT. In this article, we present our institutional approach for management of COVID-19 vaccine-related lymphadenopathy on FDG PET/CT based on our early experience. We suggest performing PET/CT at least two weeks after vaccination in patients with a cancer for which interpretation is anticipated to be potentially impacted by the vaccination, though optimally 4-6 weeks after vaccination given increased immunogenicity of mRNA vaccines and potentially longer time for resolution than lymphadenopathy after other vaccines. PET/CT should not be delayed when clinically indicated to be performed sooner. Details regarding vaccination should be collected at the time of PET/CT to facilitate interpretation. Follow-up recommendations for post-vaccination lymphadenopathy are provided, considering the lymph node's morphology and likely clinical relevance. Consideration should also be given to administering the vaccine in the arm contralateral to a unilateral cancer to avoid potentially confounding FDG uptake on the side of cancer. Our preliminary experience and suggested institutional experience should guide radiologists in the management of oncology patients undergoing PET/CT after COVID-19 vaccination.

McMahon, D. E., et al. (2021). "Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases." J Am Acad Dermatol.

BACKGROUND: Cutaneous reactions after messenger RNA (mRNA)-based COVID-19 vaccines have been reported but are not well characterized. OBJECTIVE: To evaluate the morphology and timing of cutaneous reactions after mRNA COVID-19 vaccines. METHODS: A provider-facing registry-based study collected cases of cutaneous manifestations after COVID-19 vaccination. RESULTS: From December 2020 to February 2021, we recorded 414 cutaneous reactions to mRNA COVID-19 vaccines from Moderna (83%) and Pfizer (17%). Delayed large local reactions were most common, followed by local injection site reactions, urticarial eruptions, and morbilliform eruptions. Forty-three percent of patients with first-dose reactions experienced second-dose recurrence. Additional less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions. LIMITATIONS: Registry analysis does not measure incidence. Morphologic misclassification is possible. CONCLUSIONS: We report a spectrum of cutaneous reactions after mRNA COVID-19 vaccines. We observed some dermatologic reactions to Moderna and Pfizer vaccines that mimicked SARS-CoV-2 infection itself, such as pernio/chilblains. Most patients with first-dose reactions did not have a second-dose reaction and serious adverse events did not develop in any of the patients in the registry after the first or second dose. Our data support that cutaneous reactions to COVID-19 vaccination are generally minor and self-limited, and should not discourage vaccination.

Meo, S. A., et al. (2021). "COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines." Eur Rev Med Pharmacol Sci **25**(3): 1663-1669.

OBJECTIVE: The "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)" disease has caused a worldwide challenging and threatening pandemic (COVID-19), with huge health and economic losses. The US Food and Drug Administration, (FDA) has granted emergency use authorization for treatment with the Pfizer/BioNTech and Moderna COVID-19 vaccines. Many people have a history of a significant allergic reaction to a specific food, medicine, or vaccine; hence, people all over the world have great concerns about these two authorized vaccines. This article compares the pharmacology, indications, contraindications, and adverse effects of the

Pfizer/BioNTech and Moderna vaccines. MATERIALS AND METHODS: The required documents and information were collected from the relevant databases, including Web of Science (Clarivate Analytics), PubMed, EMBASE, World Health Organization (WHO), Food and Drug Authorities (FDA) USA, Local Ministries, Health Institutes, and Google Scholar. The key terms used were: Coronavirus, SARS-COV-2, COVID-19 pandemic, vaccines, Pfizer/BioNTech vaccine, Moderna vaccine, pharmacology, benefits, allergic responses, indications, contraindications, and adverse effects. The descriptive information was recorded, and we eventually included 12 documents including research articles, clinical trials, and websites to record the required information. RESULTS: Based on the currently available literature, both vaccines are beneficial to provide immunity against SARS-CoV-2 infection. Pfizer/BioNTech Vaccine has been recommended to people 16 years of age and older, with a dose of 30 mug (0.3 m) at a cost of $19.50. It provides immunogenicity for at least 119 days after the first vaccination and is 95% effective in preventing the SARS-COV-2 infection. However, Moderna Vaccine has been recommended to people 18 years of age and older, with a dose of 50 mug (0.5 mL) at a cost of $32-37. It provides immunogenicity for at least 119 days after the first vaccination and is 94.5% effective in preventing the SARS-CoV-2 infection. However, some associated allergic symptoms have been reported for both vaccines. The COVID-19 vaccines can cause mild adverse effects after the first or second doses, including pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain, and can also rarely cause anaphylactic shock. The occurrence of adverse effects is reported to be lower in the Pfizer/BioNTech vaccine compared to the Moderna vaccine; however, the Moderna vaccine compared to the Pfizer vaccine is easier to transport and store because it is less temperature sensitive. CONCLUSIONS: The FDA has granted emergency use authorization for the Pfizer/BioNTech and Moderna COVID-19 vaccines. These vaccines can protect recipients from a SARS-CoV- 2 infection by formation of antibodies and provide immunity against a SARS-CoV-2 infection. Both vaccines can cause various adverse effects, but these reactions are reported to be less frequent in the Pfizer/BioNTech vaccine compared to the Moderna COVID-19 vaccine; however, the Moderna vaccine compared to the Pfizer vaccine is easier to transport and store because it is less temperature sensitive.

Meyer, M., et al. (2021). "mRNA-1273 efficacy in a severe COVID-19 model: attenuated activation of pulmonary immune cells after challenge." bioRxiv.

The mRNA-1273 vaccine was recently determined to be effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from interim Phase 3 results. Human studies, however, cannot provide the controlled response to infection and complex immunological insight that are only possible with preclinical studies. Hamsters are the only model that reliably exhibit more severe SARS-CoV-2 disease similar to hospitalized patients, making them pertinent for vaccine evaluation. We demonstrate that prime or prime-boost administration of mRNA-1273 in hamsters elicited robust neutralizing antibodies, ameliorated weight loss, suppressed SARS-CoV-2 replication in the airways, and better protected against disease at the highest prime-boost dose. Unlike in mice and non-human primates, mRNA-1273- mediated immunity was non-sterilizing and coincided with an anamnestic response. Single-cell RNA sequencing of lung tissue permitted high resolution analysis which is not possible in vaccinated humans. mRNA-1273 prevented inflammatory cell infiltration and the reduction of lymphocyte proportions, but enabled antiviral responses conducive to lung homeostasis. Surprisingly, infection triggered transcriptome programs in some types of immune cells from vaccinated hamsters that were shared, albeit attenuated, with mock-vaccinated hamsters. Our results support the use of mRNA-1273 in a two-dose schedule and provides insight into the potential responses within the lungs of vaccinated humans who are exposed to SARS-CoV-2.

Miao, L., et al. (2021). "mRNA vaccine for cancer immunotherapy." Mol Cancer **20**(1): 41.

mRNA vaccines have become a promising platform for cancer immunotherapy. During vaccination, naked or vehicle loaded mRNA vaccines efficiently express tumor antigens in antigen-presenting cells (APCs), facilitate APC activation and innate/adaptive immune stimulation. mRNA cancer vaccine precedes other conventional vaccine platforms due to high potency, safe administration, rapid development potentials, and cost-effective manufacturing. However, mRNA vaccine applications have been limited by instability, innate immunogenicity, and inefficient in vivo delivery. Appropriate mRNA structure modifications (i.e., codon optimizations, nucleotide modifications, self-amplifying mRNAs, etc.) and formulation methods (i.e., lipid nanoparticles (LNPs), polymers, peptides, etc.) have been investigated to overcome these issues. Tuning the administration routes and co-delivery of multiple mRNA vaccines with other immunotherapeutic agents (e.g., checkpoint inhibitors) have further boosted the host anti-tumor immunity and increased the likelihood of tumor cell eradication. With the recent U.S. Food and Drug Administration (FDA) approvals of LNP-loaded mRNA vaccines for the prevention of COVID-

19 and the promising therapeutic outcomes of mRNA cancer vaccines achieved in several clinical trials against multiple aggressive solid tumors, we envision the rapid advancing of mRNA vaccines for cancer immunotherapy in the near future. This review provides a detailed overview of the recent progress and existing challenges of mRNA cancer vaccines and future considerations of applying mRNA vaccine for cancer immunotherapies.

Milane, L. and M. Amiji (2021). "Clinical approval of nanotechnology-based SARS-CoV-2 mRNA vaccines: impact on translational nanomedicine." Drug Deliv Transl Res.

One year after the first human case of SARS-CoV-2, two nanomedicine-based mRNA vaccines have been fast-tracked, developed, and have received emergency use authorization throughout the globe with more vaccine approvals on the heels of these first two. Several SARS-CoV-2 vaccine compositions use nanotechnology-enabled formulations. A silver lining of the COVID-19 pandemic is that the fast-tracked vaccine development for SARS-CoV-2 has advanced the clinical translation pathway for nanomedicine drug delivery systems. The laboratory science of lipid-based nanoparticles was ready and rose to the clinical challenge of rapid vaccine development. The successful development and fast tracking of SARS-CoV-2 nanomedicine vaccines has exciting implications for the future of nanotechnology-enabled drug and gene delivery; it demonstrates that nanomedicine is necessary and critical to the successful delivery of advanced molecular therapeutics such as nucleic acids, it is establishing the precedent of safety and the population effect of phase four clinical trials, and it is laying the foundation for the clinical translation of more complex, non-lipid nanomedicines. The development, fast-tracking, and approval of SARS-CoV-2 nanotechnology-based vaccines has transformed the seemingly daunting challenges for clinically translating nanomedicines into measurable hurdles that can be overcome. Due to the tremendous scientific achievements that have occurred in response to the COVID-19 pandemic, years, perhaps even decades, have been streamlined for certain translational nanomedicines.

Min, Y. Q., et al. (2020). "SARS-CoV-2 nsp1: Bioinformatics, Potential Structural and Functional Features, and Implications for Drug/Vaccine Designs." Front Microbiol **11**: 587317.

The emerging coronavirus disease (COVID-19) caused by SARS-CoV-2 has led to social and economic disruption globally. It is urgently needed to understand the structure and function of the viral proteins for understanding of the viral infection and pathogenesis and development of prophylaxis and treatment strategies. Coronavirus non-structural protein 1 (nsp1) is a notable virulence factor with versatile roles in virus-host interactions and exhibits unique characteristics on sequence, structure, and function mode. However, the roles and characteristics of SARS-CoV-2 nsp1 are currently unclear. Here, we analyze the nsp1 of SARS-CoV-2 from the following perspectives: (1) bioinformatics analysis reveals that the novel nsp1 is conserved among SARS-CoV-2 strains and shares significant sequence identity with SARS-CoV nsp1; (2) structure modeling shows a 3D alpha/beta-fold of SARS-CoV-2 nsp1 highly similar to that of the SARS-CoV homolog; (3) by detailed, functional review of nsp1 proteins from other coronaviruses (especially SARS-CoV) and comparison of the protein sequence and structure, we further analyzed the potential roles of SARS-CoV-2 nsp1 in manipulating host mRNA translation, antiviral innate immunity and inflammation response and thus likely promoting viral infection and pathogenesis, which are merited to be tested in the future. Finally, we discussed how understanding of the novel nsp1 may provide valuable insights into the designs of drugs and vaccines against the unprecedented coronavirus pandemic.

Mishra, S. K. and T. Tripathi (2021). "One year update on the COVID-19 pandemic: Where are we now?" Acta Trop **214**: 105778.

We are living through an unprecedented crisis with the rapid spread of the new coronavirus disease (COVID-19) worldwide within a short time. The timely availability of thousands of SARS-CoV-2 genomes has enabled the scientific community to study the origin, structures, and pathogenesis of the virus. The pandemic has spurred research publication and resulted in an unprecedented number of therapeutic proposals. Because the development of new drugs is time consuming, several strategies, including drug repurposing and repositioning, are being tested to treat patients with COVID-19. Researchers have developed several potential vaccine candidates that have shown promise in phase II and III trials. As of 12 November 2020, 164 candidate vaccines are in preclinical evaluation, and 48 vaccines are in clinical evaluation, of which four have cleared phase III trials (Pfizer/BioNTech's BNT162b2, Moderna's mRNA-1273, University of Oxford & AstraZeneca's AZD1222, and Gamaleya's Sputnik V vaccine). Despite the acquisition of a vast body of scientific information, treatment depends only on the clinical management of the disease through supportive care. At the pandemic's 1-year mark, we summarize current information on SARS-CoV-2 origin and biology, and advances in the development of therapeutics. The updated information presented here provides a comprehensive report on the

scientific progress made in the past year in understanding of SARS-CoV-2 biology and therapeutics.

Moghimi, S. M. (2021). "Allergic Reactions and Anaphylaxis to LNP-Based COVID-19 Vaccines." Mol Ther **29**(3): 898-900.

Mohammed, M. E. A. (2021). "SARS-CoV-2 proteins: Are they useful as targets for COVID-19 drugs and vaccines?" Curr Mol Med.

The proteins of coronavirus are classified to nonstructural, structural, and accessory. There are 16 nonstructural viral proteins beside their precursors (1a and 1ab polyproteins). The nonstructural proteins are named as nsp1 to nsp16 and they act as enzymes, coenzymes, and binding proteins to facilitate the replication, transcription, and translation of the virus. The structural proteins are bound to the RNA in the nucleocapsid (N- protein) or to the lipid bilayer membrane of the viral envelope. The lipid bilayer proteins include the membrane protein (M), envelope protein (E), and spike protein (S). Beside their role as structural proteins, they are essential for the host cells binding and invasion. The SARS-CoV-2 contains six accessory proteins which participates in the viral replication, assembly and virus- host interactions. The SARS-CoV-2 accessory proteins are orf3a, orf6, orf7a, orf7b, orf8, and orf10. The functions of the SARS-CoV-2 are not well known, while the functions of their corresponding proteins in SARS-CoV are either well known or poorly studied. Recently, the Oxford University and Pfizer and BioNTech made SARS-CoV-2 vaccines through targeting the spike protein gene. The US Food and Drug Administration (FDA) and the health authorities of the United Kingdom approved and started vaccination using the Pfizer and BioNTech mRNA vaccine. Also, The FDA of USA approved the treatment of COVID-19 using two monoclonal antibodies produced by Regeneron pharmaceuticals to target the spike protein. The SARS-CoV-2 proteins can be used for the diagnosis, as drug targets and in vaccination trials for COVID-19. For future COVID-19 research, more efforts should be done to elaborate the functions and structure of the SARS-CoV-2 proteins so as to use them as targets for COVID-19 drug and vaccines. Special attention should be drawn to extensive research on the SARS-CoV-2 nsp3, orf8, and orf10.

Motta, M. (2021). "Can a COVID-19 vaccine live up to Americans' expectations? A conjoint analysis of how vaccine characteristics influence vaccination intentions." Soc Sci Med **272**: 113642.

OBJECTIVE: A vaccine for the novel coronavirus (COVID-19) could prove critical in establishing herd immunity. While past work has documented the prevalence and correlates of vaccine refusal, I assess how a less explored topic -- properties of vaccines themselves (e.g., national origin, efficacy, risk of side effects) -- might influence vaccination intentions. This information can help public health officials preempt differential intentions to vaccinate, and inform health communication campaigns that encourage vaccine uptake. RATIONALE: Previous research suggests that Americans should be more likely to intend to vaccinate if presented with a US-made vaccine that carries a low risk of minor side effects, is highly effective, is administered in just one dose, and has spent significant time in development. METHODS: I administered a conjoint experiment (N = 5940 trials) in a demographically representative survey (N = 990) of US adults to assess how variation in vaccine properties influence self-reported public vaccination intentions. RESULTS: I find that respondents prefer vaccines that are US-made, over 90% effective, and carry a less than 1% risk of minor side effects. This is potentially problematic, as some leading vaccine candidates are produced outside the US, and/or may be more likely to produce minor side effects than respondents would otherwise prefer. Worryingly, intended vaccine refusal rates exceed 30% for a vaccine meeting these optimal characteristics. Encouragingly, though, Americans show no clear preference for vaccines administered in one dose, or developed in under a year, and do not appear to draw a distinction between weakened viral vs. mRNA-based vaccines. CONCLUSION: Americans' preferences for a novel coronavirus vaccine may be at odds with the vaccine that ultimately hits the market, posing both policy and health communication challenges for vaccination uptake.

Muhammed, Y. (2020). "Molecular targets for COVID-19 drug development: Enlightening Nigerians about the pandemic and future treatment." Biosaf Health **2**(4): 210-216.

There is little or no research initiated on enlightening Nigerians about the pathogenesis, targets for drug development and repositioning for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Coronavirus disease 2019 (COVID-19) is a viral infection causing symptoms like dry cough, sore throat, nasal congestion, tiredness, fever, loss of taste, and smell etc. The disease was first reported in Wuhan, China, in December 2019. The infection is caused by SARS-CoV-2, which is the third introduction of a highly pathogenic coronavirus into the human population. Coronaviruses are viruses with a positive RNA envelope assigned to alpha, beta, gamma, and delta genera. Moreover, SARS-CoV-2 belongs to the beta genus. The four structural proteins of beta

coronavirus are membrane (M), envelope (E), spike (S), and nucleocapsid (N) protein, mediation of coronavirus host infection is established by spike (S) protein. Therefore, the search for drug development targets and repositioning of existing therapeutics is essential for fighting the present pandemic. It was reviewed that therapeutics targeting SARS-CoV-2 binding to ACE2 receptor, viral RNA synthesis and replication, 3CLpro, RdRp, and helicase will play a crucial role in the development of treatment for SARS-CoV-2 infection. Furthermore, the RdRp and spike protein of SARS-CoV-2 are the most promising targets for drug development and repositioning and vaccine development. Remdesivir combination with chloroquine/hydroxychloroquine are promising drug repositioning for the treatment of COVID-19, and mRNA-1273 targeting spike protein is the promising vaccine. However, as patient management and drug repositioning are taking place, it is imperative to identify other promising targets used by SARS-CoV-2 to establish infection, to develop novel therapeutics.

Mukhopadhyay, L., et al. (2021). "Comparison of the immunogenicity & protective efficacy of various SARS-CoV-2 vaccine candidates in non-human primates." Indian J Med Res **153**(1 & 2): 93-114.

Background & objectives: The COVID-19 pandemic has emerged as a global public health crisis and research groups worldwide are engaged in developing vaccine candidates to curb its transmission, with a few vaccines having progressed to advanced stages of clinical trials. The aim of this systematic review was to compare immunogenicity and protective efficacy of various SARS-CoV-2 vaccine candidates tested in non-human primate (NHP) models. Methods: Literature on effect of SARS-CoV-2 vaccines in NHP models reported on PubMed and preprint platforms (medRxiv and bioRxiv) till October 22, 2020, was searched with the following terms: coronavirus vaccine, COVID-19 vaccine, SARS-CoV-2 vaccine, nonhuman primate, and rhesus macaque. Results: Our search yielded 19 studies, which reported immune response elicited by 18 vaccine candidates in NHP. All the vaccines induced detectable neutralizing antibody (NAb) titres in the serum of vaccinated animals, with some showing effective viral clearance from various organs. The vaccinated animals also showed nil to mild histopathological changes in their lungs compared to placebo groups in the trials that performed necropsy. Interpretation & conclusions: Our findings highlighted onset of quick immunogenicity and protective efficacy of mRNA-1273, followed by Ad26.CoV2.S, NVX-CoV2373, BNT162b2, RBD and BBV152 vaccine candidates in preclinical trials as compared to the others. NHP data also showed correlation with clinical trial data available for a few vaccines. Preclinical trials of COVID-19 vaccine candidates in NHPs yielded promising results, with some candidates faring better than others.

Munavalli, G. G., et al. (2021). ""COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: a challenging clinical conundrum in diagnosis and treatment"." Arch Dermatol Res.

We present the first reported cases of delayed inflammatory reactions (DIR) to hyaluronic acid (HA) dermal fillers after exposure to the COVID-19 spike protein. DIR to HA is reported to occur in the different scenarios including: secondary to poor injection technique, following dental cleaning procedures, following bacterial/viral illness, and after vaccination. In this report of 4 cases with distinct clinical histories and presentations: one case occured following a community acquired COVID-19 infection, one case occured in a study subject in the mRNA-1273 clinical phase III trial, one case occurred following the first dose of publically available mRNA-1273 vaccine (Moderna, Cambridge MA), and the last case occurred after the second dose of BNT162b2 vaccine (Pfizer, New York, NY). Injectable HA dermal fillers are prevalent in aesthetic medicine for facial rejuvenation. Structural modifications in the crosslinking of HA fillers have enhanced the products' resistance to enzymatic breakdown and thus increased injected product longevity, however, have also led to a rise in DIR. Previous, DIR to HA dermal fillers can present clinically as edema with symptomatic and inflammatory erythematous papules and nodules. The mechanism of action for the delayed reaction to HA fillers is unknown and is likely to be multifactorial in nature. A potential mechanism of DIR to HA fillers in COVID-19 related cases is binding and blockade of angiotensin 2 converting enzyme receptors (ACE2), which are targeted by the SARS-CoV-2 virus spike protein to gain entry into the cell. Spike protein interaction with dermal ACE2 receptors favors a pro-inflammatory, loco-regional TH1 cascade, promoting a CD8+T cell mediated reaction to incipient granulomas, which previously formed around residual HA particles. Management to suppress the inflammatory response in the native COVID-19 case required high-dose corticosteroids (CS) to suppress inflammatory pathways, with concurrent ACE2 upregulation, along with high-dose intralesional hyaluronidase to dissolve the inciting HA filler. With regards to the two vaccine related cases; in the mRNA-1273 case, a low dose angiotensin converting enzyme inhibitor (ACE-I) was utilized for treatment, to reduce pro-inflammatory Angiotensin II. Whereas, in the BNT162b2 case the filler reaction was suppressed with oral corticosteroids. Regarding final disposition of the cases; the vaccine-

related cases returned to baseline appearance within 3 days, whereas the native COVID-19 case continued to have migratory, evanescent, periorbital edema for weeks which ultimately subsided.

Ndeupen, S., et al. (2021). "The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory." bioRxiv.

Vaccines based on mRNA-containing lipid nanoparticles (LNPs) are a promising new platform used by two leading vaccines against coronavirus disease in 2019 (COVID-19). Clinical trials and ongoing vaccinations present with very high protection levels and varying degrees of side effects. However, the nature of the reported side effects remains poorly defined. Here we present evidence that LNPs used in many preclinical studies are highly inflammatory in mice. Intradermal injection of these LNPs led to rapid and robust inflammatory responses, characterized by massive neutrophil infiltration, activation of diverse inflammatory pathways, and production of various inflammatory cytokines and chemokines. The same dose of LNP delivered intranasally led to similar inflammatory responses in the lung and resulted in a high mortality rate. In summary, here we show that the LNPs used for many preclinical studies are highly inflammatory. Thus, their potent adjuvant activity and reported superiority comparing to other adjuvants in supporting the induction of adaptive immune responses could stem from their inflammatory nature. Furthermore, the preclinical LNPs are similar to the ones used for human vaccines, which could also explain the observed side effects in humans using this platform.

Nioi, M., et al. (2020). "COVID-19 and Italian Healthcare Workers From the Initial Sacrifice to the mRNA Vaccine: Pandemic Chrono-History, Epidemiological Data, Ethical Dilemmas, and Future Challenges." Front Public Health **8**: 591900.

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic. Simultaneously, in Italy, in which the first case had occurred on February 18, the rigid phase of the lockdown began. The country has attracted worldwide attention, becoming at the same time a field of study both concerning the spread of the pandemic and advanced assessments of the effectiveness of political, public health, and therapeutic measures. The protagonists of the Italian crisis were the healthcare workers (HCWs) who were exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) without having any perception of what they were facing, courageously contributing to the containment of the epidemic to be defined by the media as "heroes." However, in the first phase of the pandemic (March-May 2020), the price that the Italian Public Health System had to pay both in terms of the number of positive virus cases and deaths among the HCWs was beyond and represented a peculiarity compared to what happened in other countries. In the current study, after a summary of the evolution of the pandemic in Italy, we offer an analysis of the statistical data concerning contagions and deaths among healthcare workers (physicians in particular). In conclusion, we describe the critical issues that still need to be resolved and the future challenges facing healthcare workers and the general population.

Nojszewska, M., et al. (2021). "COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society." Neurol Neurochir Pol **55**(1): 8-11.

A working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society has developed a statement with regard to the currently available mRNA vaccines (Pfizer-BioNTech and Moderna) preventing novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) infection, which causes Coronavirus disease 2019 (COVID-19), in patients with multiple sclerosis (MS). This statement has been based on the literature available as of 15 January, 2021. The guidance will be updated as new data emerges. All data regarding the above-mentioned vaccines comes from clinical trials which have been reviewed, published and approved by the regulatory authorities [1, 2]. In the current manuscript, whenever a SARS-CoV-2 vaccine is discussed, it refers to mRNA vaccines only.

Noor, R. (2021). "Developmental Status of the Potential Vaccines for the Mitigation of the COVID-19 Pandemic and a Focus on the Effectiveness of the Pfizer-BioNTech and Moderna mRNA Vaccines." Curr Clin Microbiol Rep: 1-8.

Purpose of Review: Along with the continued in silico-based studies for drug designing and repurposing followed by the corresponding cell culture studies, the ongoing clinical trials with some completed regarding finding the drug efficacy and the vaccine development against the severe acute respiratory coronavirus 2 (SARS-CoV-2) have been the most functional and indispensable issue during the current COVID-19 pandemic within 2020 and onward. The present review attempted to figure out the update on this effective vaccine and discussed the other promising vaccines. Recent findings: A range of investigations on the SARS-CoV-2 genomics, on its similarities with SARS-CoV-1, and with the Middle

East respiratory syndrome coronavirus (MERS-CoV) have been accomplished and the host immune dodging mechanisms by the SARS-CoV-2 have been unraveled which in turn led the scientists around the world to work rigorously on the vaccine development. Working with various vaccine platforms so far revealed the efficacy of the mRNA-1273 vaccine as the most effective one as resulted through the clinical trials which resulted in 95% positive output. Summary: Although currently commercialized mRNA-1273 vaccine appears to be effective, still several points are to be pondered regarding the sustainability of vaccine efficacy against the rising variants of SARS-CoV-2.

Ohadian Moghadam, S. (2020). "A Review on Currently Available Potential Therapeutic Options for COVID-19." Int J Gen Med **13**: 443-467.

A series of unexplained pneumonia cases currently were first reported in December 2019 in Wuhan, China. Official names have been announced for the virus responsible, previously known as "2019 novel coronavirus" and the diseases it causes are, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19), respectively. Despite great efforts worldwide to control SARS-CoV-2, the spread of the virus has reached a pandemic. Infection prevention and control of this virus is the primary concern of public health officials and professionals. Currently, several therapeutic options for COVID-19 are proposed and vaccine development has been initiated for prevention purposes. In this review, we will discuss the most recent evidence about the current potential treatment options including anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, nucleoside analogs, protease inhibitors, monoclonal antibodies, and convalescent plasma therapy. Some other agents such as vitamin D and melatonin, which were recommended as potential adjuvant treatments for COVID-19 infection are also presented. Moreover, the potential use of convalescent plasma for treatment of COVID-19 infection was described. Furthermore, in the next part of the current review, various vaccination approaches against COVID-19 including whole virus vaccines, recombinant subunit vaccine, DNA vaccines, and mRNA vaccines are discussed.

Oliver, S. E., et al. (2020). "The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020." MMWR Morb Mortal Wkly Rep **69**(50): 1922-1924.

On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine (Pfizer, Inc; Philadelphia, Pennsylvania), a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the prefusion spike glycoprotein of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19) (1). Vaccination with the Pfizer-BioNTech COVID-19 vaccine consists of 2 doses (30 mug, 0.3 mL each) administered intramuscularly, 3 weeks apart. On December 12, 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation* for use of the Pfizer-BioNTech COVID-19 vaccine in persons aged >/=16 years for the prevention of COVID-19. To guide its deliberations regarding the vaccine, ACIP employed the Evidence to Recommendation (EtR) Framework,(dagger) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.(section sign) The recommendation for the Pfizer-BioNTech COVID-19 vaccine should be implemented in conjunction with ACIP's interim recommendation for allocating initial supplies of COVID-19 vaccines (2). The ACIP recommendation for the use of the Pfizer-BioNTech COVID-19 vaccine under EUA is interim and will be updated as additional information becomes available.

Oliver, S. E., et al. (2021). "The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine - United States, December 2020." MMWR Morb Mortal Wkly Rep **69**(5152): 1653-1656.

On December 18, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Moderna COVID-19 (mRNA-1273) vaccine (ModernaTX, Inc; Cambridge, Massachusetts), a lipid nanoparticle-encapsulated, nucleoside-modified mRNA vaccine encoding the stabilized prefusion spike glycoprotein of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19) (1). This vaccine is the second COVID-19 vaccine authorized under an EUA for the prevention of COVID-19 in the United States (2). Vaccination with the Moderna COVID-19 vaccine consists of 2 doses (100 mug, 0.5 mL each) administered intramuscularly, 1 month (4 weeks) apart. On December 19, 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation* for use of the Moderna COVID-19 vaccine in persons aged >/=18 years for the prevention of COVID-19. To guide its deliberations regarding the vaccine, ACIP employed the Evidence to Recommendation (EtR) Framework,(dagger) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.(section sign) Use of all COVID-19 vaccines authorized under an EUA, including the Moderna COVID-19 vaccine, should be implemented in conjunction with ACIP's interim

recommendations for allocating initial supplies of COVID-19 vaccines (3). The ACIP recommendation for the use of the Moderna COVID-19 vaccine under EUA is interim and will be updated as additional information becomes available.

Onyeaka, H., et al. (2021). "A review on the advancements in the development of vaccines to combat coronavirus disease 2019." Clin Exp Vaccine Res **10**(1): 6-12.

Coronavirus disease 2019 (COVID-19), the deadly disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a global pandemic that has severely affected lives and economies around the globe. The spread of this virus will be very difficult to contain if no vaccine is ready for implementation. This is because of the high human-to-human transmission rate of this virus and the fact that the virus is in the community spread stage. As of 31st August 2020, 25.3 million individuals have been affected by this deadly virus resulting in about 850,673 deaths. To combat the spread of COVID-19, more than 100 applicant immunizations are being developed around the world. Among them, eight have begun or will be soon beginning preliminary clinical trials. This paper provides a review of the current developments of potential COVID-19 vaccines around the world. It specifically discusses the recombinant vaccine produced by the University of Oxford and AstraZeneca (Cambridge, UK), the use of novel self-amplifying RNA technique to create a vaccine and the progress made by UNAID (US National Institute of Allergy and Infectious Diseases) and World Health Organization (WHO). Furthermore, this review demonstrates the pharmaceutical prophylaxis and treatment protocols for COVID-19 by analysing the documentation set up by the WHO for up to date data with respect to the novel coronavirus of 2019-2020.

Ophinni, Y., et al. (2020). "COVID-19 Vaccines: Current Status and Implication for Use in Indonesia." Acta Med Indones **52**(4): 388-412.

The coronavirus disease 2019 (COVID-19) has inflicted catastrophic damages in public health, economic and social stability-putting life globally on hold in 2020 and presumably a year more. Indonesia bears a heavy burden of the pandemic, counting the highest case prevalence and fatality rate in all of Southeast Asia. One hope remains in the groundbreaking universal effort in search of a vaccine against the causative virus SARS-CoV-2, which has shown success unparalleled in human vaccine development thus far. An array of modalities including novel techniques are being utilized as vaccine platforms, with the closest to phase III clinical trial completion being mRNA (manufactured by Moderna and BioNTech/Pfizer), inactivated virus (Sinovac, Sinopharm), viral vector (Oxford/AstraZeneca, Gamaleya, Janssen/Johnson&Johnson, CanSino), and protein subunit (Novavax). The vaccine produced by BioNTech/Pfizer has been deployed to the public as the first ever licensed COVID-19 vaccine. In this review, we will review all of these modalities on their safety and immunogenicity, phase II/III trial results of the nine vaccine candidates and current situation as of 29 December 2020, as well as the implication for use and distribution in Indonesia. COVID-19 vaccine progress, however, is moving exceedingly fast and new advances are unfolding on a daily basis, to which we hope an update to this review can be published in early 2021.

Pal, R., et al. (2021). "COVID-19 vaccination in patients with diabetes mellitus: Current concepts, uncertainties and challenges." Diabetes Metab Syndr **15**(2): 505-508.

BACKGROUND AND AIMS: To summarize the available evidence on the use COVID-19 vaccines in patients with diabetes mellitus. METHODS: We performed a thorough literature search with regard to COVID-19 vaccines in patients with type 1 and type 2 diabetes mellitus. RESULTS: The novel coronavirus disease (COVID-19) tends to portend a poor prognosis in patients with diabetes mellitus (DM). Primary prevention remains the mainstay for mitigating the risks associated with COVID-19 in patients with DM. A significant step in primary prevention is timely vaccination. Routine vaccination against pneumococcal pneumonia, influenza, and hepatitis B is recommended in patients with DM with good efficacy and reasonable safety profile. With clinical data supporting a robust neutralizing antibody response in COVID-19 patients with DM, vaccination in individuals with DM is justified. In fact, as the burden of the disease is borne by people with DM, COVID-19 vaccination should be prioritized in individuals with DM. Multiple unresolved issues with regard to preferred vaccine type, vaccine efficacy and durability, frequency of administration, vaccination in children (<18 years) and pregnant/lactating women however remain, and need to be addressed through future research. CONCLUSIONS: Patients with type 1 and type 2 diabetes mellitus are at a high risk of poor prognosis with COVID-19 and vaccination should be prioritized in them. However, many unresolved issues with regard to COVID-19 vaccination need to be addressed through future research.

Parasher, A. (2021). "COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment." Postgrad Med J **97**(1147): 312-320.

BACKGROUND: The severe acute

respiratory syndrome (SARS) coronavirus-2 is a novel coronavirus belonging to the family Coronaviridae and is now known to be responsible for the outbreak of a series of recent acute atypical respiratory infections originating in Wuhan, China. The disease caused by this virus, termed coronavirus disease 19 or simply COVID-19, has rapidly spread throughout the world at an alarming pace and has been declared a pandemic by the WHO on March 11, 2020. In this review, an update on the pathophysiology, clinical presentation and the most recent management strategies for COVID-19 has been described. MATERIALS AND METHODS: A search was conducted for literature and various articles/case reports from 1997 to 2020 in PUBMED/MEDLINE for the keywords coronavirus, SARS, Middle East respiratory syndrome and mRNA virus. RESULTS AND CONCLUSIONS: COVID-19 has now spread globally with increasing morbidity and mortality among all populations. In the absence of a proper and effective antibody test, the diagnosis is presently based on a reverse-transcription PCR of nasopharyngeal and oropharyngeal swab samples. The clinical spectrum of the disease presents in the form of a mild, moderate or severe illness. Most patients are either asymptomatic carriers who despite being without symptoms have the potential to be infectious to others coming in close contact, or have a mild influenza-like illness which cannot be differentiated from a simple upper respiratory tract infection. Moderate and severe cases require hospitalisation as well as intensive therapy which includes non-invasive as well as invasive ventilation, along with antipyretics, antivirals, antibiotics and steroids. Complicated cases may require treatment by immunomodulatory drugs and plasma exchange therapy. The search for an effective vaccine for COVID-19 is presently in full swing, with pharmaceutical corporations having started human trials in many countries.

Park, J. W., et al. (2021). "mRNA vaccines for COVID-19: what, why and how." Int J Biol Sci **17**(6): 1446-1460.

The Coronavirus disease-19 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2), has impacted human lives in the most profound ways with millions of infections and deaths. Scientists and pharmaceutical companies have been in race to produce vaccines against SARS-CoV-2. Vaccine generation usually demands years of developing and testing for efficacy and safety. However, it only took less than one year to generate two mRNA vaccines from their development to deployment. The rapid production time, cost-effectiveness, versatility in vaccine design, and clinically proven ability to induce cellular and humoral immune response have crowned mRNA vaccines with spotlights as most promising vaccine candidates in the fight against the pandemic. In this review, we discuss the general principles of mRNA vaccine design and working mechanisms of the vaccines, and provide an up-to-date summary of pre-clinical and clinical trials on seven anti-COVID-19 mRNA candidate vaccines, with the focus on the two mRNA vaccines already licensed for vaccination. In addition, we highlight the key strategies in designing mRNA vaccines to maximize the expression of immunogens and avoid intrinsic innate immune response. We also provide some perspective for future vaccine development against COVID-19 and other pathogens.

Park, K. S., et al. (2021). "Non-viral COVID-19 vaccine delivery systems." Adv Drug Deliv Rev **169**: 137-151.

The novel corona virus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread throughout the globe at a formidable speed, causing tens of millions of cases and more than one million deaths in less than a year of its report in December 2019. Since then, companies and research institutions have raced to develop SARS-CoV-2 vaccines, ranging from conventional viral and protein-based vaccines to those that are more cutting edge, including DNA- and mRNA-based vaccines. Each vaccine exhibits a different potency and duration of efficacy, as determined by the antigen design, adjuvant molecules, vaccine delivery platforms, and immunization method. In this review, we will introduce a few of the leading non-viral vaccines that are under clinical stage development and discuss delivery strategies to improve vaccine efficacy, duration of protection, safety, and mass vaccination.

Parums, D. V. (2021). "Editorial: SARS-CoV-2 mRNA Vaccines and the Possible Mechanism of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)." Med Sci Monit **27**: e932899.

During 2020 and 2021, the global pandemic of coronavirus disease 2019 (COVID-19) due to severe acute respi- ratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in high death rates and acute and chronic morbidity in all countries. The rapid development of new mRNA vaccines to SARS-CoV-2 brings hope that the spread of this virus can be controlled. The ChAdOx1 nCoV-19 vaccine developed by a collaboration between the University of Oxford and AstraZeneca showed efficacy in clinical trials, with a good safety profile. However, there have been recent reports of the rare development of thrombotic events in young women following vaccination with ChAdOx1 nCoV-19, particularly of the rare condition of cavernous sinus thrombosis. Studies have begun to in-vestigate whether antibodies to the SARS-CoV-2 spike

cross-react with platelet factor 4 (PF4/CXLC4) and mim- ic autoimmune heparin-induced thrombocytopenia. This Medical Science Monitor Editorial aims to briefly update the current status of studies on a possible rare complication of using new mRNA vaccines to prevent COVID-19.

Pascolo, S. (2021). "Synthetic Messenger RNA-Based Vaccines: from Scorn to Hype." Viruses **13**(2).

In the race for a vaccine against SARS-CoV-2, the synthetic mRNA format has been shown to be the fastest one and proved to be safe and highly efficient, even at the very low dose of a few microg per injection. The mRNA vaccines are not new: vaccines that are based on attenuated mRNA viruses, such as Mumps, Measles, and Rubella, immunize by delivering their mRNAs into the cells of the vaccinated individual, who produces the viral proteins that then prime the immune response. Synthetic mRNA in liposomes can be seen as a modern, more refined, and thereby a safer version of those live attenuated RNA viruses. The anti-COVID-19 mRNA vaccine (coding the SARS-CoV-2 spike protein) is the third synthetic RNA therapeutic being approved. It follows the aptamer Macugen((R)) (which neutralizes VEGF) and the siRNA Onpattro((R)) (which destroys the transthyretin-coding mRNA). Remarkably, the 30 microg of mRNA that are contained in the first approved anti-COVID-19 vaccine are sufficient for generating high levels of neutralizing antibodies against the virus in all injected volunteers (including participants over 65 years old). The efficacy and safety data are stunning. The distribution of these vaccines throughout the world will bring a halt to the coronavirus pandemic.

Paul, G. and R. Chad (2021). "Newborn antibodies to SARS-CoV-2 detected in cord blood after maternal vaccination - a case report." BMC Pediatr **21**(1): 138.

BACKGROUND: Maternal vaccination for Influenza and Tetanus, Diphtheria, acellular Pertussis (TDaP) have been well studied in terms of safety and efficacy for protection of the newborn by placental passage of antibodies. Similar newborn protection would be expected after maternal vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19). There is a significant and urgent need for research regarding safety and efficacy of vaccination against SARS-CoV-2 during pregnancy. CASE PRESENTATION: A vigorous, healthy, full-term female was born to a COVID-19 naive mother who had received a single dose of messenger RNA (mRNA) vaccine for SARS-CoV-2 3 weeks prior to delivery. IgG cord blood antibodies were detected to SARS-CoV-2 at the time of birth. CONCLUSION: Here, we report the first known case of an infant with SARS-CoV-2 IgG antibodies detectable in cord blood after maternal vaccination.

Pepperrell, T., et al. (2021). "Making a COVID-19 vaccine that works for everyone: ensuring equity and inclusivity in clinical trials." Glob Health Action **14**(1): 1892309.

Coronavirus disease 2019 (COVID-19) mortality and morbidity have been shown to increase with deprivation and impact non-White ethnicities more severely. Despite the extra risk Black, Asian and Minority Ethnicity (BAME) groups face in the pandemic, our current medical research system seems to prioritise innovation aimed at people of European descent. We found significant difficulties in assessing baseline demographics in clinical trials for COVID-19 vaccines, displaying a lack of transparency in reporting. Further, we found that most of these trials take place in high-income countries, with only 25 of 219 trials (11.4%) taking place in lower middle- or low-income countries. Trials for the current best vaccine candidates (BNT162b2, ChadOx1, mRNA-173) recruited 80.0% White participants. Underrepresentation of BAME groups in medical research will perpetuate historical distrust in healthcare processes, and poses a risk of unknown differences in efficacy and safety of these vaccines by phenotype. Limiting trial demographics and settings will mean a lack of global applicability of the results of COVID-19 vaccine trials, which will slow progress towards ending the pandemic.

Peter, J. (2021). "COVID-19 vaccination: Recommendations for management of patients with allergy or immune-based diseases." S Afr Med J **111**(4): 291-294.

As South Africa continues to battle the second wave of SARS-CoV-2 infections, the imminent arrival of vaccines against COVID-19 offers hope. Vaccine roll-out has been accompanied by heightened media coverage that has created both excitement and anxiety, reporting on the shortened timeline of vaccine trials and approvals, as well as the recent series of anaphylaxis cases associated with the two approved mRNA COVID-19 vaccines. Patients with allergic and other immune-based diseases are subgroups especially concerned about vaccine safety and efficacy. This practice guideline offers broad recommendations for COVID-19 vaccination in various subgroups of allergic and immunebased disease, highlighting risk/benefit evaluation, and where and how routine vaccination should be altered.

Phylactou, M., et al. (2021). "Characteristics of endothelial corneal transplant rejection following immunisation with SARS-CoV-2 messenger RNA vaccine." Br J Ophthalmol.

AIM: We report two cases of endothelial corneal allograft rejection following immunisation with SARS-CoV-2 messenger RNA (mRNA) vaccine BNT162b2 and describe the implications for management of transplant recipients postvaccination for COVID-19. METHODS: A 66-year-old woman with Fuchs endothelial corneal dystrophy (FECD) and a unilateral Descemet's membrane endothelial keratoplasty (DMEK) transplant received COVID-19 mRNA vaccine BNT162b2 14 days post-transplant. Seven days later, she presented with symptoms and signs of endothelial graft rejection. An 83-year-old woman with bilateral DMEK transplants for FECD 3 and 6 years earlier developed simultaneous acute endothelial rejection in both eyes, 3 weeks post second dose of COVID-19 mRNA vaccine BNT162b2. Rejection in both cases was treated successfully with topical corticosteroids. CONCLUSIONS: We believe this is the first report of temporal association between corneal transplant rejection following immunisation against COVID-19 and the first report of DMEK rejection following any immunisation. We hypothesise that the allogeneic response may have been initiated by the host antibody response following vaccination. Clinicians and patients should be aware of the potential of corneal graft rejection associated with vaccine administration and may wish to consider vaccination in advance of planned non-urgent keratoplasties. Patients should be counselled on the symptoms and signs that require urgent review to allow early treatment of any confirmed rejection episode.

Plotkin, S. A. and N. Halsey (2021). "Accelerate COVID-19 Vaccine Rollout by Delaying the Second Dose of mRNA Vaccines." Clin Infect Dis.

Prubeta, B. M. (2021). "Current State of the First COVID-19 Vaccines." Vaccines (Basel) **9**(1).

SARS CoV-2 and its associated disease COVID-19 has devastated the world during 2020. Masks and social distancing could be efficient if done by large proportions of the population, but pandemic fatigue has decreased their efficacy. Economic shut downs come with large price tags and cannot be a long term solution either. The announcements by three vaccine manufacturers in November that their vaccines are 90% or more effective has given hope to at least those in the population who plan to get vaccinated as soon as a scientifically and medically sound vaccine becomes available. This review summarizes the underlying design strategies and current status of development of the nine vaccines that were in phase III trial on 8 November 2020. Contracts between vaccine manufacturing companies and governments aim at distributing the vaccine to a large part of the world population. Questions remain how the temperature sensitive mRNA vaccines will be transported and/or stored and how vaccination will be prioritized within each country. Additionally, current contracts do not cover all countries, with a serious gap in Africa and South America. The second part of this review will detail current distribution plans and remaining challenges with vaccine accessibility and acceptance.

Putter, J. S. (2021). "Immunotherapy for COVID-19: Evolving treatment of viral infection and associated adverse immunological reactions." Transfus Apher Sci **60**(2): 103093.

This review on COVID-19 immunotherapy enables a comparative analysis of the short-list of currently approved major vaccines. These include the Pfizer and Moderna first mRNA vaccines under FDA purview and the Oxford/AstraZeneca simian adenovirus-vectored vaccine (under UK-MHPRA guidance), all produced in record time, being safe and effective. The Pfizer and Moderna double dose vaccines have the clear edge in treatment efficacy, being in the 90% range compared to AstraZeneca in the average 70%. However, the AZ double dose vaccine has significant advantages with respect to lower cost and stability in storage. We enumerate several potential advances in the technology of the manufacturers: (1) combination vaccines such as testing AstraZeneca's product with a component of the Russian's Sputnik V to achieve durable immunity; (2) the potential for single dose vaccines coming on-line, and with Johnson & Johnson/Janssen; and (3) the need for refined thermotolerant formulations obviating the need for cold storage. As an adjunct to vaccinotherapy, affinity adsorption column technology is another facet recruited in the processing of corona convalescent plasma/cryosupernatant to concentrate neutralizing antibodies against the virus. Clinical trials, to date, of infected patients have been indeterminate as to whether plasmapheresis-based products are effective or not. This is due to the failure to standardize the composition of the plasma derived component, ambiguous clinical indications for use in human subjects, and inconsistent timing of administration in the course of the infection. Known T-cell lymphopenia, which is attendant to progressive viral infection and immune driven inflammation, may be a quantitative surrogate biological marker as to when to start treatment. This is not only for initiating plasmapheresis-based therapeutics but also the judicious selection of ancillary pharmaceuticals, ie. monoclonal antibodies, recombinant proteins and anti-viral drugs.

Quer, G., et al. (2021). "The Physiologic Response to COVID-19 Vaccination." medRxiv.

Two mRNA vaccines and one adenovirus-based vaccine against SARS CoV-2 are currently being

distributed at scale in the United States. Objective evidence of a specific individual's physiologic response to that vaccine are not routinely tracked but may offer insights into the acute immune response and personal and/or vaccine characteristics associated with that. We explored this possibility using a smartphone app-based research platform developed early in the pandemic that enabled volunteers (38,911 individuals between 25 March 2020 and 4 April 2021) to share their smartwatch and activity tracker data, as well as self-report, when appropriate, any symptoms, COVID-19 test results and vaccination dates and type. Of 4,110 individuals who reported at least one mRNA vaccination dose, 3,312 provided adequate resting heart rate data from the peri-vaccine period for analysis. We found changes in resting heart rate with respect to an individual baseline increased the days after vaccination, peaked on day 2, and returned to normal on day 6, with a much stronger effect after second dose with respect to first dose (average changes 1.6 versus 0.5 beats per minute). The changes were more pronounced for individuals who received the Moderna vaccine (on both doses), those who previously tested positive to COVID-19 (on dose 1), and for individuals aged <40 years, after adjusting for possible confounding factors. Taking advantage of continuous passive data from personal sensors could potentially enable the identification of a digital fingerprint of inflammation, which might prove useful as a surrogate for vaccine-induced immune response.

Rabinowich, L., et al. (2021). "Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients." J Hepatol.

BACKGROUND AND AIMS: Two SARS-CoV-2 mRNA vaccines were approved to prevent COVID-19 infection, with reported vaccine efficacy of 95%. Liver transplant (LT) recipients are at risk for lower vaccine immunogenicity and were not included in the registration trials. We assessed vaccine immunogenicity and safety in this special population. METHODS: LT recipients followed at the Tel-Aviv Sourasky Medical Center and healthy volunteers were tested for SARS-CoV-2 IgG antibodies directed against the Spike-protein (S) and Nucleocapsid-protein (N) 10-20 days after receiving the second Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine dose. Information regarding vaccine side effects and clinical data was collected from patients and medical records. RESULTS: Eighty LT recipients were enrolled. Mean age was 60 years and 30% were female. Twenty-five healthy volunteer controls were younger (mean age 52.7 years, p=0.013) and mostly female (68%, p=0.002). All participants were negative for IgG N-protein serology, indicating immunity did not result from prior COVID-19 infection. All controls were positive for IgG S-protein serology. Immunogenicity among LT recipients was significantly lower with positive serology in only 47.5% (p<0.001). Antibody titer was also significantly lower in this group (mean 95.41 AU/mL vs. 200.5 AU/mL in controls, p<0.001). Predictors for negative response among LT recipients were older age, lower eGFR, and treatment with high dose steroids and MMF. No serious adverse events were reported in both groups. CONCLUSION: LT recipients developed substantially lower immunological response to Pfizer-BioNTech SARS-CoV-2 mRNA-based vaccine. Factors influencing serological antibodies response include age, renal function and immunosuppressive medications. The findings require re-evaluation of vaccine regimens in this population. LAY SUMMARY: Liver Transplant recipients had a substantially inferior immunity to the Pfizer-BioNTech BNT162b2 SARS-CoV-2 vaccine. Less than half of the patients developed sufficient levels of antibodies against the virus, and in those who were positive, average antibody levels were two times less compared to healthy controls. Factors predicting non-response were older age, renal function and immunosuppressive medications.

Rahman, M. S., et al. (2020). "Epitope-based chimeric peptide vaccine design against S, M and E proteins of SARS-CoV-2, the etiologic agent of COVID-19 pandemic: an in silico approach." PeerJ **8**: e9572.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiologic agent of the ongoing pandemic of coronavirus disease 2019 (COVID-19), a public health emergency of international concerns declared by the World Health Organization (WHO). An immuno-informatics approach along with comparative genomics was applied to design a multi-epitope-based peptide vaccine against SARS-CoV-2 combining the antigenic epitopes of the S, M, and E proteins. The tertiary structure was predicted, refined and validated using advanced bioinformatics tools. The candidate vaccine showed an average of >/=90.0% world population coverage for different ethnic groups. Molecular docking and dynamics simulation of the chimeric vaccine with the immune receptors (TLR3 and TLR4) predicted efficient binding. Immune simulation predicted significant primary immune response with increased IgM and secondary immune response with high levels of both IgG1 and IgG2. It also increased the proliferation of T-helper cells and cytotoxic T-cells along with the increased IFN-gamma and IL-2 cytokines. The codon optimization and mRNA secondary structure prediction revealed that the chimera is suitable for high-level expression and cloning. Overall, the constructed recombinant chimeric vaccine candidate demonstrated significant potential and can be considered for clinical validation to fight

against this global threat, COVID-19.

Rama, T. A., et al. (2021). "mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis." J Allergy Clin Immunol **147**(3): 877-878.

Rapp, A. R., et al. (2021). "Methods matter - Tailoring SARS-CoV-2 antibody targets to vaccination status." Clin Chim Acta **519**: 140-141.

Individuals who have been vaccinated for COVID19 should have IgG antibody in response to the specific antigen that is the target in the vaccine development. There are several options for targeted COVID19 antigen, but most manufacturers have focused on the spike protein. Using our understanding of the targeted antigen for vaccine development, we can develop testing algorithmic scheme for anti-spike and anti-nucleocapsid antibody assays to aid delineation of infection versus vaccination in our patient population. Clear communication from laboratories specifying the specific SARS-CoV-2 antibodies (i.e., anti-spike, anti-nucleocapsid, or both) in their antibody tests at both the ordering and reporting levels will play crucial role in the development of this approach and is essential to avoid potential provider/patient confusion in the interpretation of serologic testing.

Rego, G. N. A., et al. (2020). "Current Clinical Trials Protocols and the Global Effort for Immunization against SARS-CoV-2." Vaccines (Basel) **8**(3).

Coronavirus disease 2019 (COVID-19) is the biggest health challenge of the 21st century, affecting millions of people globally. The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has ignited an unprecedented effort from the scientific community in the development of new vaccines on different platforms due to the absence of a broad and effective treatment for COVID-19 or prevention strategy for SARS-CoV-2 dissemination. Based on 50 current studies selected from the main clinical trial databases, this systematic review summarizes the global race for vaccine development against COVID-19. For each study, the main intervention characteristics, the design used, and the local or global center partnerships created are highlighted. Most vaccine developments have taken place in Asia, using a viral vector method. Two purified inactivated SARS-CoV-2 vaccine candidates, an mRNA-based vaccine mRNA1273, and the chimpanzee adenoviral vaccine ChAdOx1 are currently in phase III clinical trials in the respective countries Brazil, the United Arab Emirates, the USA, and the United Kingdom. These vaccines are being developed based on a quickly formed network of collaboration.

Rele, S. (2021). "COVID-19 vaccine development during pandemic: gap analysis, opportunities, and impact on future emerging infectious disease development strategies." Hum Vaccin Immunother **17**(4): 1122-1127.

The world remains cautiously optimistic about a COVID-19 vaccine that is relatively safe and efficacious and that offers sufficient long-lasting protection/immunity by neutralizing the virus infectivity. However, key technical hurdles pertaining to antigen-adjuvant formulation, delivery, and manufacturing challenges of lipid nanoparticles (LNPs) for mRNA vaccines and stability of formulations need to be addressed for successful product development and stockpiling. In addition, the dosage form, the dosage level and regimen for eliciting a protective immune response remain to be established. The high dependence of global supply chains and demand-supply to sourcing quality raw materials, glassware and other supplies, along with the stress on existing production capacities and platform-specific manufacturing challenges could impede vaccine development and access. This article provides critical analysis of vaccine development processes and unit operations that can derail the pandemic response, and also extends to other emerging infectious disease development efforts - issues that take on added significance given the global mandate for an accelerated and at-risk development path to tackle the COVID-19 pandemic.

Rice, A. M., et al. (2021). "Evidence for Strong Mutation Bias toward, and Selection against, U Content in SARS-CoV-2: Implications for Vaccine Design." Mol Biol Evol **38**(1): 67-83.

Large-scale re-engineering of synonymous sites is a promising strategy to generate vaccines either through synthesis of attenuated viruses or via codon-optimized genes in DNA vaccines. Attenuation typically relies on deoptimization of codon pairs and maximization of CpG dinucleotide frequencies. So as to formulate evolutionarily informed attenuation strategies that aim to force nucleotide usage against the direction favored by selection, here, we examine available whole-genome sequences of SARS-CoV-2 to infer patterns of mutation and selection on synonymous sites. Analysis of mutational profiles indicates a strong mutation bias toward U. In turn, analysis of observed synonymous site composition implicates selection against U. Accounting for dinucleotide effects reinforces this conclusion, observed UU content being a quarter of that expected under neutrality. Possible mechanisms of selection against U mutations include selection for higher expression, for high mRNA

stability or lower immunogenicity of viral genes. Consistent with gene-specific selection against CpG dinucleotides, we observe systematic differences of CpG content between SARS-CoV-2 genes. We propose an evolutionarily informed approach to attenuation that, unusually, seeks to increase usage of the already most common synonymous codons. Comparable analysis of H1N1 and Ebola finds that GC3 deviated from neutral equilibrium is not a universal feature, cautioning against generalization of results.

Risma, K. A., et al. (2021). "Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines." J Allergy Clin Immunol.

Anaphylaxis to vaccines is historically a rare event. The coronavirus disease 2019 pandemic drove the need for rapid vaccine production applying a novel antigen delivery system: messenger RNA vaccines packaged in lipid nanoparticles. Unexpectedly, public vaccine administration led to a small number of severe allergic reactions, with resultant substantial public concern, especially within atopic individuals. We reviewed the constituents of the messenger RNA lipid nanoparticle vaccine and considered several contributors to these reactions: (1) contact system activation by nucleic acid, (2) complement recognition of the vaccine-activating allergic effector cells, (3) preexisting antibody recognition of polyethylene glycol, a lipid nanoparticle surface hydrophilic polymer, and (4) direct mast cell activation, coupled with potential genetic or environmental predispositions to hypersensitivity. Unfortunately, measurement of anti-polyethylene glycol antibodies in vitro is not clinically available, and the predictive value of skin testing to polyethylene glycol components as a coronavirus disease 2019 messenger RNA vaccine-specific anaphylaxis marker is unknown. Even less is known regarding the applicability of vaccine use for testing (in vitro/vivo) to ascertain pathogenesis or predict reactivity risk. Expedient and thorough research-based evaluation of patients who have suffered anaphylactic vaccine reactions and prospective clinical trials in putative at-risk individuals are needed to address these concerns during a public health crisis.

Rogliani, P., et al. (2021). "SARS-CoV-2 Neutralizing Antibodies: A Network Meta-Analysis across Vaccines." Vaccines (Basel) **9**(3).

Background: There are no studies providing head-to-head comparison across SARS-CoV-2 vaccines. Therefore, we compared the efficacy of candidate vaccines in inducing neutralizing antibodies against SARS-CoV-2. Methods: A network meta-analysis was performed to compare the peak levels of SARS-CoV-2 neutralizing antibodies across candidate vaccines. Data were reported as standardized mean difference (SMD) since the outcome was assessed via different metrics and methods across the studies. Results: Data obtained from 836 healthy adult vaccine recipients were extracted from 11 studies. BBIBP-CorV, AZD1222, BNT162b2, New Crown COVID-19, and Sputnik V induced a very large effect on the level of neutralizing antibodies (SMD > 1.3); CoVLP, CoronaVac, NVX-CoV2373, and Ad5-nCoV induced a large effect (SMD > 0.8 to </=1.3); and Ad26.COV2.S induced a medium effect (SMD > 0.5 to </=0.8). BBIBP-CorV and AZD122 were more effective ($p < 0.05$) than Ad26.COV2.S, Ad5-nCoV, mRNA-1237, CoronaVac, NVX-CoV2373, CoVLP, and New Crown COVID-19; New Crown COVID-19 was more effective ($p < 0.05$) than Ad26.COV2.S, Ad5-nCoV, and mRNA-1237; CoronaVac was more effective ($p < 0.05$) than Ad26.COV2.S and Ad5-nCoV; and Sputnik V and BNT162b2 were more effective ($p < 0.05$) than Ad26.COV2.S. In recipients aged </=60 years, AZD1222, BBIBP-CorV, and mRNA-1237 were the most effective candidate vaccines. Conclusion: All the candidate vaccines induced significant levels of SARS-CoV-2 neutralizing antibodies, but only AZD1222 and mRNA-1237 were certainly tested in patients aged >/=70 years. Compared with AZD1222, BNT162b and mRNA-1237 have the advantage that they can be quickly re-engineered to mimic new mutations of SARS-CoV-2.

Roltgen, K., et al. (2021). "mRNA vaccination compared to infection elicits an IgG-predominant response with greater SARS-CoV-2 specificity and similar decrease in variant spike recognition." medRxiv.

During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, new vaccine strategies including lipid nanoparticle delivery of antigen encoding RNA have been deployed globally. The BioNTech/Pfizer mRNA vaccine BNT162b2 encoding SARS-CoV-2 spike protein shows 95% efficacy in preventing disease, but it is unclear how the antibody responses to vaccination differ from those generated by infection. Here we compare the magnitude and breadth of antibodies targeting SARS-CoV-2, SARS-CoV-2 variants of concern, and endemic coronaviruses, in vaccinees and infected patients. We find that vaccination differs from infection in the dominance of IgG over IgM and IgA responses, with IgG reaching levels similar to those of severely ill COVID-19 patients and shows decreased breadth of the antibody response targeting endemic coronaviruses. Viral variants of concern from B.1.1.7 to P.1 to B.1.351 form a remarkably consistent hierarchy of progressively decreasing antibody recognition by both vaccinees and infected patients exposed to Wuhan-Hu-1 antigens.

Rosa, S. S., et al. (2021). "mRNA vaccines manufacturing: Challenges and bottlenecks." Vaccine **39**(16): 2190-2200.

Vaccines are one of the most important tools in public health and play an important role in infectious diseases control. Owing to its precision, safe profile and flexible manufacturing, mRNA vaccines are reaching the stoplight as a new alternative to conventional vaccines. In fact, mRNA vaccines were the technology of choice for many companies to combat the Covid-19 pandemic, and it was the first technology to be approved in both United States and in Europe Union as a prophylactic treatment. Additionally, mRNA vaccines are being studied in the clinic to treat a number of diseases including cancer, HIV, influenza and even genetic disorders. The increased demand for mRNA vaccines requires a technology platform and cost-effective manufacturing process with a well-defined product characterisation. Large scale production of mRNA vaccines consists in a 1 or 2-step in vitro reaction followed by a purification platform with multiple steps that can include Dnase digestion, precipitation, chromatography or tangential flow filtration. In this review we describe the current state-of-art of mRNA vaccines, focusing on the challenges and bottlenecks of manufacturing that need to be addressed to turn this new vaccination technology into an effective, fast and cost-effective response to emerging health crises.

Rosenberg, H. F. and P. S. Foster (2021). "Eosinophils and COVID-19: diagnosis, prognosis, and vaccination strategies." Semin Immunopathol.

The unprecedented impact of the coronavirus disease 2019 (COVID-19) pandemic has resulted in global challenges to our health-care systems and our economic security. As such, there has been significant research into all aspects of the disease, including diagnostic biomarkers, associated risk factors, and strategies that might be used for its treatment and prevention. Toward this end, eosinopenia has been identified as one of many factors that might facilitate the diagnosis and prognosis of severe COVID-19. However, this finding is neither definitive nor pathognomonic for COVID-19. While eosinophil-associated conditions have been misdiagnosed as COVID-19 and others are among its reported complications, patients with pre-existing eosinophil-associated disorders (e.g., asthma, eosinophilic gastrointestinal disorders) do not appear to be at increased risk for severe disease; interestingly, several recent studies suggest that a diagnosis of asthma may be associated with some degree of protection. Finally, although vaccine-associated aberrant inflammatory responses, including eosinophil accumulation in the respiratory tract, were observed in preclinical immunization studies targeting the related SARS-CoV and MERS-CoV pathogens, no similar complications have been reported clinically in response to the widespread dissemination of either of the two encapsulated mRNA-based vaccines for COVID-19.

Rusk, D. S., et al. (2021). "Lack of immune response after mRNA vaccination to SARS-CoV-2 in a solid organ transplant patient." J Med Virol.

The recent approval and distribution of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been a major development in the fight against the current coronavirus disease 2019 (COVID-19) pandemic. The first two vaccines approved in the United States, mRNA-1273, and BNT162b2, are both messenger RNA (mRNA) based and highly effective in immunocompetent persons, but efficacy in patients on immunosuppressants has not been established. Additionally, data suggests these patients are less likely than immunocompetent people to develop neutralizing antibodies after COVID-19 infection. Given the high risk of poor outcomes in organ transplant and immunosuppressed patients, effective vaccination is paramount in this group. We present the first reported case of a solid organ transplant patient who failed to achieve seroconversion after two doses of mRNA vaccine. This case has significant implications about how immunosuppressed patients should be counseled about SARS-CoV-2 vaccination and the protection provided. Physicians should remain clinically suspicious for infection with SARS-CoV-2 despite vaccination status in solid organ transplant patients.

Rzymski, P., et al. (2021). "The Perception and Attitudes toward COVID-19 Vaccines: A Cross-Sectional Study in Poland." Vaccines (Basel) **9**(4).

Vaccine hesitancy is a major threat to the success of COVID-19 vaccination programs. The present cross-sectional online survey of adult Poles (n = 1020) expressing a willingness to receive the COVID-19 vaccine was conducted between February and March 2021 and aimed to assess (i) the general trust in different types of vaccines, (ii) the level of acceptance of the COVID-19 vaccines already in use in Poland (BNT162b2 by BioNTech/Pfizer, mRNA-1273 by Moderna and AZD1222 by Oxford/AstraZeneca) as well as eight vaccines approved outside European Union (EU) or in advanced stages of clinical trials, (iii) level of fear of vaccination against COVID-19, and (iv) main sources of information on COVID-19 vaccination. Among all major vaccine technology, the highest level of trust was observed for the mRNA platform, with a considerable number of surveyed (>20%) not aware of the existence of vaccines produced using the traditional approach (inactivated and live attenuated vaccines).

The age of participants was the main factor differentiating the level of trust in a particular vaccine type. Both BNT162b and mRNA-1273 received a high level of acceptance, contrary to AZD1222. From eight vaccines unauthorized in the EU at the moment of study, the CVnCoV (mRNA; CureVac) was met with the highest level of trust, followed by Ad26.COV2.S (vector; Janssen/Johnson&Johnson) and NVX-CoV2373 (protein; Novavax). Sputnik V (vector; Gamaleya Research Institute) was decidedly the least trusted vaccine. The median level of fear (measured by the 10-point Likert-type scale) in the studied group was 4.0, mostly related to the risk of serious allergic reactions, other severe adverse events and unknown long-term effects of vaccination. Female, individuals with a lower level of education and those not seeking any information on the COVID-19 vaccines revealed a higher fear of vaccination. Experts' materials were the major source of information on COVID-19 vaccines in the studied group. The study shows the level of trust in COVID-19 vaccines can vary much across the producers while the mRNA vaccines are received with a high level of acceptance. It also emphasizes the need for effective and continuous science communication when fighting the pandemic as it may be an ideal time to increase the general awareness of vaccines.

Salazar, P., et al. (2021). "High coverage COVID-19 mRNA vaccination rapidly controls SARS-CoV-2 transmission in Long-Term Care Facilities." Res Sq.

Residents of Long-Term Care Facilities (LTCFs) represent a major share of COVID-19 deaths worldwide. Information on vaccine effectiveness in these settings is essential to improve mitigation strategies, but evidence remains limited. To evaluate the early effect of the administration of BNT162b2 mRNA vaccines in LTCFs, we monitored subsequent SARS-CoV-2 documented infections and deaths in Catalonia, a region of Spain, and compared them to counterfactual model predictions from February 6th to March 28th, 2021, the subsequent time period after which 70% of residents were fully vaccinated. We calculated the reduction in SARS-CoV-2 documented infections and deaths as well as the detected county-level transmission. We estimated that once more than 70% of the LTCFs population were fully vaccinated, 74% (58%-81%, 90% CI) of COVID-19 deaths and 75% (36%-86%) of all documented infections were prevented. Further, detectable transmission was reduced up to 90% (76-93% 90%CI). Our findings provide evidence that high-coverage vaccination is the most effective intervention to prevent SARS-CoV-2 transmission and death. Widespread vaccination could be a feasible avenue to control the COVID-19 pandemic.

Salmeron Rios, S., et al. (2021). "Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study." J Am Geriatr Soc.

BACKGROUND/OBJECTIVES: The safety and immunogenicity of the BNT162b2 coronavirus disease 2019 (COVID-19) vaccine in older adults with different frailty and disability profiles have not been well determined. Our objective was to analyze immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in older adults across frailty and disability profiles. DESIGN: Multicenter longitudinal cohort study. SETTING AND PARTICIPANTS: A total of 134 residents aged >/=65 years with different frailty and disability profiles in five long-term care facilities (LTCFs) in Albacete, Spain. INTERVENTION AND MEASUREMENTS: Residents were administered two vaccine doses as per the label, and antibody levels were determined 21.9 days (SD 9.3) after both the first and second dose. Functional variables were assessed using activities of daily living (Barthel Index), and frailty status was determined with the FRAIL instrument. Cognitive status and comorbidity were also evaluated. RESULTS: Mean age was 82.9 years (range 65-99), and 71.6% were female. The mean antibody titers in residents with and without previous COVID-19 infection were 49,878 AU/ml and 15,274 AU/ml, respectively (mean difference 34,604; 95% confidence interval [CI]: 27,699-41,509). No severe adverse reactions were observed, after either vaccine dose. Those with prevaccination COVID-19 had an increased antibody level after the vaccine (B = 31,337; 95% CI: 22,725-39,950; $p < 0.001$). Frailty, disability, older age, sex, cognitive impairment, or comorbidities were not associated with different antibody titers. CONCLUSIONS: The BNT162b2 mRNA COVID-19 vaccine in older adults is safe and produces immunogenicity, independently of the frailty and disability profiles. Older adults in LTCFs should receive a COVID-19 vaccine.

Samanovic, M. I., et al. (2021). "Poor antigen-specific responses to the second BNT162b2 mRNA vaccine dose in SARS-CoV-2-experienced individuals." medRxiv.

The advent of COVID-19 vaccines will play a major role in helping to end the pandemic that has killed millions worldwide. Vaccine candidates have demonstrated robust humoral responses and have protected against infection. However, efficacy trials were focused on individuals with no prior exposure to SARS-CoV-2, and, as a result, little is known about immune responses induced by these mRNA vaccines in individuals who recovered from COVID-19. Here, we evaluated immune responses in 32 subjects who received two-dose BNT162b2 mRNA vaccination. In individuals naive to SARS-CoV-2, we observed robust

increases in humoral and antigen-specific antibody-secreting cell (ASC) responses following each dose of vaccine, whereas individuals with prior exposure to SARS-CoV-2 demonstrated strong humoral and antigen-specific ASC responses to the first dose but muted responses to the second dose of the vaccine for the time points studied. These data highlight an important gap in our knowledge and may have major implications for how these vaccines should be used to prevent COVID-19. One sentence summary: Immune responses to the booster dose of mRNA vaccine BNT162b2 are poor in subjects with a prior history of SARS-CoV-2 infection.

Sandbrink, J. B. and R. J. Shattock (2020). "RNA Vaccines: A Suitable Platform for Tackling Emerging Pandemics?" Front Immunol **11**: 608460.

The COVID-19 pandemic demonstrates the ongoing threat of pandemics caused by novel, previously unrecognized, or mutated pathogens with high transmissibility. Currently, vaccine development is too slow for vaccines to be used in the control of emerging pandemics. RNA-based vaccines might be suitable to meet this challenge. The use of an RNA-based delivery mechanism promises fast vaccine development, clinical approval, and production. The simplicity of in vitro transcription of mRNA suggests potential for fast, scalable, and low-cost manufacture. RNA vaccines are safe in theory and have shown acceptable tolerability in first clinical trials. Immunogenicity of SARS-CoV-2 mRNA vaccines in phase 1 trials looks promising, however induction of cellular immunity needs to be confirmed and optimized. Further optimization of RNA vaccine modification and formulation to this end is needed, which may also enable single injection regimens to be achievable. Self-amplifying RNA vaccines, which show high immunogenicity at low doses, might help to improve potency while keeping manufacturing costs low and speed high. With theoretical properties of RNA vaccines looking promising, their clinical efficacy is the key remaining question with regard to their suitability for tackling emerging pandemics. This question might be answered by ongoing efficacy trials of SARS-CoV-2 mRNA vaccines.

Sanicas, M., et al. (2020). "A review of COVID-19 vaccines in development: 6 months into the pandemic." Pan Afr Med J **37**: 124.

The advent of the COVID-19 pandemic and the dynamics of its spread is unprecedented. Therefore, the need for a vaccine against the virus is huge. Researchers worldwide are working around the clock to find a vaccine. Experts estimate that a fast-tracked vaccine development process could speed a successful candidate to market in approximately 12-18 months. The objective of this review was to describe the coronavirus vaccines candidates in development and the important considerations. The review was conducted through a thematic analysis of the literature on COVID-19 vaccines in development. It only included data until the end of June 2020, 6 months after the emergence of the COVID-19. Different approaches are currently used to develop COVID-19 vaccines from traditional live-attenuated, inactivated, subunit vaccines, to more novel technologies such as DNA or mRNA vaccines. The race is on to find both medicines and vaccines for the COVID-19 pandemic. As with drugs, vaccine candidates go through pre-clinical testing first before they go through the three phases of clinical trials in humans. Of the over 130 vaccine candidates, 17 are in clinical trials while others are expected to move to clinical testing after the animal studies.

Schoenmaker, L., et al. (2021). "mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability." Int J Pharm **601**: 120586.

A drawback of the current mRNA-lipid nanoparticle (LNP) COVID-19 vaccines is that they have to be stored at (ultra)low temperatures. Understanding the root cause of the instability of these vaccines may help to rationally improve mRNA-LNP product stability and thereby ease the temperature conditions for storage. In this review we discuss proposed structures of mRNA-LNPs, factors that impact mRNA-LNP stability and strategies to optimize mRNA-LNP product stability. Analysis of mRNA-LNP structures reveals that mRNA, the ionizable cationic lipid and water are present in the LNP core. The neutral helper lipids are mainly positioned in the outer, encapsulating, wall. mRNA hydrolysis is the determining factor for mRNA-LNP instability. It is currently unclear how water in the LNP core interacts with the mRNA and to what extent the degradation prone sites of mRNA are protected through a coat of ionizable cationic lipids. To improve the stability of mRNA-LNP vaccines, optimization of the mRNA nucleotide composition should be prioritized. Secondly, a better understanding of the milieu the mRNA is exposed to in the core of LNPs may help to rationalize adjustments to the LNP structure to preserve mRNA integrity. Moreover, drying techniques, such as lyophilization, are promising options still to be explored.

Sciarrone Alibrandi, M. T., et al. (2021). "[Covid-19 vaccination and renal patients: overcoming unwarranted fears and re-establishing priorities]." G Ital Nefrol **38**(2).

The SARS-CoV-2 (Covid-19) has infected about 124 million people worldwide and the total amount of casualties now sits at a staggering 2.7

million. One enigmatic aspect of this disease is the protean nature of the clinical manifestations, ranging from total absence of symptoms to extremely severe cases with multiorgan failure and death. Chronic Kidney Disease (CKD) has emerged as the primary risk factor in the most severe patients, apart from age. Kidney disease and acute kidney injury have been correlated with a higher risk of death. Notably the Italian Society of Nephrology have reported a 10-fold increase in mortality in patients undergoing dialysis compared to the rest of the population, especially during the second phase of the pandemic (26% vs 2.4). These dramatic numbers require an immediate response. At the moment of writing, three Covid-19 vaccines are being administered already , two of which, Pfizer-BioNTech and Moderna, share the same mRNA mechanism and Vaxzevria (AstraZeneca) based on a more traditional approach. All of them are completely safe and reliable. The AIFA scientific commission has suggested that the mRNA vaccines should be administered to older and more fragile patients, while the Vaxzevria (AstraZeneca) vaccine should be reserved for younger subjects above the age of 18. The near future looks bright: there are tens of other vaccines undergoing clinical and preclinical validation, whose preliminary results look promising. The high mortality of CKD and dialysis patients contracting Covid-19 should mandate top priority for their vaccination.

Shaker, M., et al. (2021). "The Importance of a Timely Second Dose of the 2021 COVID-19 mRNA Vaccine Depends on the Protection Afforded by a First Dose and Subsequent Risk of Anaphylaxis." J Allergy Clin Immunol Pract.

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents our greatest hope to combat the devastating coronavirus disease 2019 (COVID-19) pandemic. Amid ongoing global vaccination efforts, rare cases of severe allergic reactions to COVID-19 mRNA vaccines have received significant attention. Although the exact nature of these reactions may be heterogeneous, various approaches exist to engage with patients, communities, public health departments, primary care providers, and other clinicians in a multidisciplinary approach to advance population health. Whereas it is optimal for patients to receive COVID-19 vaccination as outlined in emergency use authorizations, second-dose deferral of mRNA vaccines may be a consideration within a shared decision-making paradigm of care in select circumstances characterized by high durable first-vaccine-dose protection and significant elevations of vaccine anaphylaxis risk. Still, the durability of protection afforded by a single dose of a COVID-19 mRNA vaccine is uncertain, and alternative approaches to complete vaccination, including precautionary use of a COVID-19 viral vector vaccine, also remain patient-preference-sensitive options. There is an urgent need to define correlates of COVID-19 immunity and the level of longer-term protection afforded by COVID-19 vaccination.

Shen, X., et al. (2021). "SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines." Cell Host Microbe **29**(4): 529-539 e523.

All current vaccines for COVID-19 utilize ancestral SARS-CoV-2 spike with the goal of generating protective neutralizing antibodies. The recent emergence and rapid spread of several SARS-CoV-2 variants carrying multiple spike mutations raise concerns about possible immune escape. One variant, first identified in the United Kingdom (B.1.1.7, also called 20I/501Y.V1), contains eight spike mutations with potential to impact antibody therapy, vaccine efficacy, and risk of reinfection. Here, we show that B.1.1.7 remains sensitive to neutralization, albeit at moderately reduced levels (approximately sim;2-fold), by serum samples from convalescent individuals and recipients of an mRNA vaccine (mRNA-1273, Moderna) and a protein nanoparticle vaccine (NVX-CoV2373, Novavax). A subset of monoclonal antibodies to the receptor binding domain (RBD) of spike are less effective against the variant, while others are largely unaffected. These findings indicate that variant B.1.1.7 is unlikely to be a major concern for current vaccines or for an increased risk of reinfection.

Shi, Y., et al. (2020). "[Progress and challenge of vaccine development against 2019-novel coronavirus (2019-nCoV)]." Zhonghua Yu Fang Yi Xue Za Zhi **54**(6): 614-619.

The outbreak of 2019-novel coronavirus (2019-nCoV) infection poses a serious threat to global public health. Vaccination is an effective way to prevent the epidemic of the virus. 2019-nCoV along with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) belong to the same beta-genus of coronavirus family. Basing on the previous experience and the technical platform of developing SARS-CoV and MERS-CoV vaccines, scientists from all over the world are working hard and quickly on the related fields. There are substantial progress in these fields including characterizing the 2019-nCoV virus, identification of candidate antigens and epitopes, establishment of animal models, characterizing the immune responses, and the design of vaccines. The development of 2019-nCoV vaccines covers all types: inactivated virus vaccine, recombinant protein vaccine, viral vector-based vaccine, mRNA vaccine, and DNA

vaccine, et al. As of March 2020, two 2019-nCoV vaccines have entered phase I clinical trials. One is named as Ad5-nCoV developed by the Chinese Institute of Biotechnology of the Academy of Military Medical Sciences and Tianjin Cansino Biotechnology Inc. Ad5-nCoV is based on the replication-defective adenovirus type 5 as the vector to express 2019-nCoV spike protein. The another vaccine is mRNA-1273 developed by the National Institute of Allergy and Infectious Diseases and Moderna, Inc.. RNA-1273 is an mRNA vaccine expressing 2019-nCoV spike protein. Although the rapid development of 2019-nCoV vaccine, it still faces many unknown challenges, including the antigenic characteristics of the 2019-nCoV, the influence of antigenic variation, the protective immune response of host, the protection of the elderly population, and the downstream manufacturing process of the new vaccine. The safety and efficacy of vaccines are the first priority for vaccine development and should be carefully evaluated.

Shin, M. D., et al. (2020). "COVID-19 vaccine development and a potential nanomaterial path forward." Nat Nanotechnol **15**(8): 646-655.

The COVID-19 pandemic has infected millions of people with no clear signs of abatement owing to the high prevalence, long incubation period and lack of established treatments or vaccines. Vaccines are the most promising solution to mitigate new viral strains. The genome sequence and protein structure of the 2019-novel coronavirus (nCoV or SARS-CoV-2) were made available in record time, allowing the development of inactivated or attenuated viral vaccines along with subunit vaccines for prophylaxis and treatment. Nanotechnology benefits modern vaccine design since nanomaterials are ideal for antigen delivery, as adjuvants, and as mimics of viral structures. In fact, the first vaccine candidate launched into clinical trials is an mRNA vaccine delivered via lipid nanoparticles. To eradicate pandemics, present and future, a successful vaccine platform must enable rapid discovery, scalable manufacturing and global distribution. Here, we review current approaches to COVID-19 vaccine development and highlight the role of nanotechnology and advanced manufacturing.

Simonetti, O., et al. (2021). "Safety and Efficacy of Vaccines during COVID-19 Pandemic in Patients Treated with Biological Drugs in a Dermatological Setting." Healthcare (Basel) **9**(4).

The BNT162b2 and mRNA-1273 vaccines, consisting of mRNA, have recently become available. The absolute novelty of these vaccines introduces questions about their safety and efficacy, especially in patients who are treated with biological drugs in dermatology. The aim of our review was to provide a broad overview of the current use of all available vaccinations in concomitance with biological therapy and to suggest indications for the new mRNA Covid-19 vaccines. We conducted a narrative review of the literature regarding the indications and safety of the various types of vaccines currently available in dermatological patients treated with biological therapy. The safety and efficacy of administering inactivated vaccines in patients undergoing biological therapy with inhibitors of TNF-alpha, IL-17, IL-12/23, and IL-4/13 was confirmed. Inactivated vaccines can be administered during therapy with inhibitors of IL-23 and IgE, taking into account that the level of evidence is lower due to the lack of specific studies. Live attenuated vaccines were contraindicated in concomitance with all biological therapies considered, except omalizumab. According to this evidence, we assume that there are currently no contraindications to the administration of the new Covid-19 BNT162b2 and mRNA-1273 vaccines during biological therapy with inhibitors of TNF-alpha, IL-17, IL-12/23, IL-23, and IL-4/13, since these vaccines are comparable to inactivated ones. For patients with chronic urticaria or allergic asthma treated with omalizumab, we currently recommend caution in using the mRNA Covid-19 vaccines (30 min observation). The only contraindications were a previous history of hypersensitivity to the Covid-19 vaccines themself or to their excipients. In conclusion, further randomized clinical trials are needed to evaluate the efficacy of the antibody response in these patients.

Sivaganesh, V., et al. (2021). "Emerging Immunotherapies against Novel Molecular Targets in Breast Cancer." Int J Mol Sci **22**(5).

Immunotherapy is a highly emerging form of breast cancer therapy that enables clinicians to target cancers with specific receptor expression profiles. Two popular immunotherapeutic approaches involve chimeric antigen receptor-T cells (CAR-T) and bispecific antibodies (BsAb). Briefly mentioned in this review as well is the mRNA vaccine technology recently popularized by the COVID-19 vaccine. These forms of immunotherapy can highly select for the tumor target of interest to generate specific tumor lysis. Along with improvements in CAR-T, bispecific antibody engineering, and therapeutic administration, much research has been done on novel molecular targets that can especially be useful for triple-negative breast cancer (TNBC) immunotherapy. Combining emerging immunotherapeutics with tumor marker discovery sets the stage for highly targeted immunotherapy to be the future of cancer treatments. This review highlights the principles of CAR-T and BsAb therapy, improvements in CAR and BsAb

engineering, and recently identified human breast cancer markers in the context of in vitro or in vivo CAR-T or BsAb treatment.

Smetanova, J., et al. (2020). "Principles and new perspectives in the vaccination against SARS-CoV-2 virus." Cas Lek Cesk **159**(7-8): 298-302.

It has been a year since the first person on Earth became infected with a new type of coronavirus SARS-CoV-2, causing infectious acute respiratory disease COVID-19 with relatively high morbidity and mortality. The most endangered population by coronavirus SARS-CoV-2 are healthcare professionals, the elderly and people with associated comorbidities. Due to the fast community spread, governments of different European countries introduced precaution measures including limited socializing of people, closing of most public services and introducing mandatory facial protection. The hope for a return to the life before the pandemic is the development of an effective and safe vaccine against SARS-CoV-2 which would presumably reduce the incidence of severe forms of COVID-19 and prevent the massive spread of the disease. At the end of November, we have 13 clinical trials in phase III involving SARS-CoV-2 vaccines based on inactivated viruses, recombinant non-pathogenic viral vectors and proteins. The first mRNA-based vaccine is currently being evaluated in phase II/III clinical trial and is already being distributed and applied to high-risk population in the United Kingdom, the United States, and Israel, followed by the countries of the European Union, including the Czech Republic. In the review article we present currently ongoing clinical studies with a special focus on the phase III clinical trials and discuss the mechanisms of action of each type of vaccine.

Sokolowska, M., et al. (2021). "EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines." Allergy.

The first approved COVID-19 vaccines include Pfizer/BioNTech BNT162B2, Moderna mRNA-1273 and AstraZeneca recombinant adenoviral ChAdOx1-S. Soon after approval, severe allergic reactions to the mRNA-based vaccines that resolved after treatment were reported. Regulatory agencies from the European Union, Unites States and the United Kingdom agree that vaccinations are contraindicated only when there is an allergy to one of the vaccine components or if there was a severe allergic reaction to the first dose. This position paper of the European Academy of Allergy and Clinical Immunology (EAACI) agrees with these recommendations and clarifies that there is no contraindication to administer these vaccines to allergic patients who do not have a history of an allergic reaction to any of the vaccine components. Importantly, as is the case for any medication, anaphylaxis may occur after vaccination in the absence of a history of allergic disease. Therefore, we provide a simplified algorithm of prevention, diagnosis and treatment of severe allergic reactions and a list of recommended medications and equipment for vaccine centres. We also describe potentially allergenic/immunogenic components of the approved vaccines and propose a workup to identify the responsible allergen. Close collaboration between academia, regulatory agencies and vaccine producers will facilitate approaches for patients at risks, such as incremental dosing of the second injection or desensitisation. Finally, we identify unmet research needs and propose a concerted international roadmap towards precision diagnosis and management to minimise the risk of allergic reactions to COVID-19 vaccines and to facilitate their broader and safer use.

Soleimanpour, S. and A. Yaghoubi (2021). "COVID-19 vaccine: where are we now and where should we go?" Expert Rev Vaccines **20**(1): 23-44.

INTRODUCTION: The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has currently caused the pandemic with a high progressive speed and has been considered as the global public health crisis in 2020. This new member of the coronavirus family has created a potentially fatal disease, called coronavirus disease-2019 (COVID-19). Despite the continuous efforts of researchers to find effective vaccines and drugs for COVID-19, there is still no success in this matter. AREAS COVERED: Here, the literature regarding the COVID-19 vaccine candidates currently in the clinical trials, as well as main candidates in pre-clinical stages for development and research, were reviewed. These candidates have been developed under five different major platforms, including live-attenuated vaccine, mRNA-based vaccine, DNA vaccines, inactivated virus, and viral-vector-based vaccine. EXPERT OPINION: There are several limitations in the field of the rapid vaccine development against SARS-CoV-2, and other members of the coronavirus family such as SARS-CoV and MERS-CoV. The key challenges of designing an effective vaccine within a short time include finding the virulence ability of an emerging virus and potential antigen, choosing suitable experimental models and efficient route of administration, the immune-response study, designing the clinical trials, and determining the safety, as well as efficacy.

Stafford, I. A., et al. (2021). "The coronavirus disease 2019 vaccine in pregnancy: risks, benefits, and recommendations." Am J Obstet Gynecol **224**(5): 484-495.

The coronavirus disease 2019 has caused over

2 million deaths worldwide, with over 412,000 deaths reported in Unites States. To date, at least 57,786 pregnant women in the United States have been infected, and 71 pregnant women have died. Although pregnant women are at higher risk of severe coronavirus disease 2019-related illness, clinical trials for the available vaccines excluded pregnant and lactating women. The safety and efficacy of the vaccines for pregnant women, the fetus, and the newborn remain unknown. A review of maternal and neonatal coronavirus disease 2019 morbidity and mortality data along with perinatal vaccine safety considerations are presented to assist providers with shared decision-making regarding vaccine administration for this group, including the healthcare worker who is pregnant, lactating, or considering pregnancy. The coronavirus disease 2019 vaccine should be offered to pregnant women after discussing the lack of safety data, with preferential administration for those at highest risk of severe infection, until safety and efficacy of these novel vaccines are validated.

Sumirtanurdin, R. and M. I. Barliana (2021). "Coronavirus Disease 2019 Vaccine Development: An Overview." Viral Immunol **34**(3): 134-144.

To this day, the coronavirus disease 2019 (COVID-19) pandemic has not shown signs of abating. Moreover, the virus responsible for the pandemic, severe acute respiratory syndrome coronavirus 2, has evolved into three different variants. This phenomenon highlights an even greater need to develop drugs and vaccines to control the rate of infection and spread of the disease. As of July 7, 2020, at least 160 vaccine candidates, 21 of which have entered the clinical trial phase, have been developed. This article describes the latest advances in development, reliable platforms, strategies used, and challenges that remain in developing COVID-19 vaccines.

Talukder, P. and S. Chanda (2021). "RNAi Technology and Investigation on Possible Vaccines to Combat SARS-CoV-2 Infection." Appl Biochem Biotechnol.

Coronavirus disease of 2019 (COVID-19) pandemic, taking place globally, occurs as a result of the SARS-CoV-2 viral infection which has caused death of innumerable numbers of people and is responsible for a massive drop in the global economy. Millions of people are infected, and the death rate is also quite high in different countries. So, there is an urgent requirement of the invention of some effective and efficient drugs that can be effective against this deadly viral infection. The invention of new drugs and vaccine has become a matter of utmost importance to stop the mayhem of coronavirus pandemic. In the middle of such a deadly pandemic, the necessity of development of a vaccine is of high importance in this context. Among all the popular methods of vaccine development, the mRNA vaccines turned out to be the one of the most versatile vaccine with quick responses. However, in this review, we have explained all the possible types of vaccines available including DNA vaccines, RNA vaccines, and live and attenuated vaccines. Their effectiveness, importance, and application of the vaccines against the SARS-CoV-2 virus have been discussed. Research is also being conducted in the field of gene silencing, and one of the best possible ways to combat the virus at the molecular level is by applying RNAi technology. The modified siRNA molecules can be used to silence the gene expression of the virus. A summarization of the virus's behavior, characteristics, and the methods by which RNAi technology can be administered to control the virus is depicted in this study.

Tande, A. J., et al. (2021). "Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening." Clin Infect Dis.

BACKGROUND: Several vaccines are now clinically available under emergency use authorization in the United States and have demonstrated efficacy against symptomatic COVID-19. The impact of vaccines on asymptomatic SARS-CoV-2 infection is largely unknown. METHODS: We conducted a retrospective cohort study of consecutive, asymptomatic adult patients (n = 39,156) within a large United States healthcare system who underwent 48,333 pre-procedural SARS-CoV-2 molecular screening tests between December 17, 2020 and February 8, 2021. The primary exposure of interest was vaccination with at least one dose of an mRNA COVID-19 vaccine. The primary outcome was relative risk of a positive SARS-CoV-2 molecular test among those asymptomatic persons who had received at least one dose of vaccine, as compared to persons who had not received vaccine during the same time period. Relative risk was adjusted for age, sex, race/ethnicity, patient residence relative to the hospital (local vs. non-local), healthcare system regions, and repeated screenings among patients using mixed effects log-binomial regression. RESULTS: Positive molecular tests in asymptomatic individuals were reported in 42 (1.4%) of 3,006 tests performed on vaccinated patients and 1,436 (3.2%) of 45,327 tests performed on unvaccinated patients (RR=0.44 95% CI: 0.33-0.60; p<.0001). Compared to unvaccinated patients, the risk of asymptomatic SARS-CoV-2 infection was lower among those >10 days after 1 st dose (RR=0.21; 95% CI: 0.12-0.37; p<.0001) and >0 days after 2 nd dose (RR=0.20; 95% CI: 0.09-0.44; p<.0001) in the adjusted analysis. CONCLUSIONS: COVID-19 vaccination with an mRNA-based vaccine showed a significant association with a reduced risk of

asymptomatic SARS-CoV-2 infection as measured during pre-procedural molecular screening. The results of this study demonstrate the impact of the vaccines on reduction in asymptomatic infections supplementing the randomized trial results on symptomatic patients.

Tang, W., et al. (2021). "SARS-CoV-2 vaccines in patients with SLE." Lupus Sci Med **8**(1).

As the Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) vaccines become available to patients with autoimmune diseases and SLE, practitioners will have to inform them about the safety and efficacy of these vaccines. Here we discuss the challenges of applying vaccine data to patients with autoimmune diseases and the evidence available in the literature that may help in the decision process.

Tanmay, S., et al. (2021). "Is SARS-CoV-2 Spike glycoprotein impairing macrophage function via alpha7-nicotinic acetylcholine receptors?" Food Chem Toxicol **152**: 112184.

The innate immune cells play an important role in handling early infections, and can eliminate them completely up to a certain threshold. Beyond that threshold they take up their role in "The Resolution of Inflammation". The recognition of the SARS-CoV-2 antigen triggers an eicosanoid storm and initiates a robust inflammatory response. This establishes a positive feedback loop which develops into a sustained cytokine storm which interferes with the activation of adaptive immune cells. The mechanism of this interaction, and hence the pathogenesis of the virus with the immune system, is yet to be determined. In silico studies predict a direct SARS-CoV-2 spike glycoprotein interaction with nicotinic acetylcholine receptors, which could impair macrophage function and initiate the cascade of events in severe infections. We here, add to the hypothesis that immune dysregulation can be caused by the interaction of the SARS-CoV-2 spike glycoprotein via a cryptic epitope with the alpha7-nAChR in Type-1 macrophages, discuss its implications for the treatment of COVID-19 patients, and present better prospects for the design and dissemination of more effective vaccines and their importance.

Team, C. C.-R., et al. (2021). "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 **70**(4): 125-129.

As of January 20, 2021, a total of 24,135,690 cases of coronavirus disease 2019 (COVID-19) and 400,306 associated deaths had been reported in the United States (https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days). On December 18, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Moderna COVID-19 vaccine administered as 2 doses, 1 month apart to prevent COVID-19. On December 19, 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of Moderna COVID-19 vaccine (1). As of January 10, 2021, a reported 4,041,396 first doses of Moderna COVID-19 vaccine had been administered in the United States, and reports of 1,266 (0.03%) adverse events after receipt of Moderna COVID-19 vaccine were submitted to the Vaccine Adverse Event Reporting System (VAERS). Among these, 108 case reports were identified for further review as possible cases of severe allergic reaction, including anaphylaxis. Anaphylaxis is a life-threatening allergic reaction that occurs rarely after vaccination, with onset typically within minutes to hours (2). Among these case reports, 10 cases were determined to be anaphylaxis (a rate of 2.5 anaphylaxis cases per million Moderna COVID-19 vaccine doses administered), including nine in persons with a documented history of allergies or allergic reactions, five of whom had a previous history of anaphylaxis. The median interval from vaccine receipt to symptom onset was 7.5 minutes (range = 1-45 minutes). Among eight persons with follow-up information available, all had recovered or been discharged home. Among the remaining case reports that were determined not to be anaphylaxis, 47 were assessed to be nonanaphylaxis allergic reactions, and 47 were considered nonallergic adverse events. For four case reports, investigators have been unable to obtain sufficient information to assess the likelihood of anaphylaxis. This report summarizes the clinical and epidemiologic characteristics of case reports of allergic reactions, including anaphylaxis and nonanaphylaxis allergic reactions, after receipt of the first dose of Moderna COVID-19 vaccine during December 21, 2020-January 10, 2021, in the United States. CDC has issued updated interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States (3) and interim considerations for preparing for the potential management of anaphylaxis (4).

Team, C. C.-R., et al. (2021). "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 **70**(2): 46-51.

As of January 3, 2021, a total of 20,346,372 cases of coronavirus disease 2019 (COVID-19) and 349,246 associated deaths have been reported in the United States. Long-term sequalae of COVID-19 over the course of a lifetime currently are unknown; however, persistent symptoms and serious

complications are being reported among COVID-19 survivors, including persons who initially experience a mild acute illness.* On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Pfizer-BioNTech COVID-19 vaccine to prevent COVID-19, administered as 2 doses separated by 21 days. On December 12, 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine (1); initial doses were recommended for health care personnel and long-term care facility residents (2). As of December 23, 2020, a reported 1,893,360 first doses of Pfizer-BioNTech COVID-19 vaccine had been administered in the United States, and reports of 4,393 (0.2%) adverse events after receipt of Pfizer BioNTech COVID-19 vaccine had been submitted to the Vaccine Adverse Event Reporting System (VAERS). Among these, 175 case reports were identified for further review as possible cases of severe allergic reaction, including anaphylaxis. Anaphylaxis is a life-threatening allergic reaction that does occur rarely after vaccination, with onset typically within minutes to hours (3). Twenty-one cases were determined to be anaphylaxis (a rate of 11.1 per million doses administered), including 17 in persons with a documented history of allergies or allergic reactions, seven of whom had a history of anaphylaxis. The median interval from vaccine receipt to symptom onset was 13 minutes (range = 2-150 minutes). Among 20 persons with follow-up information available, all had recovered or been discharged home. Of the remaining case reports that were determined not to be anaphylaxis, 86 were judged to be nonanaphylaxis allergic reactions, and 61 were considered nonallergic adverse events. Seven case reports were still under investigation. This report summarizes the clinical and epidemiologic characteristics of case reports of allergic reactions, including anaphylaxis and nonanaphylaxis allergic reactions, after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine during December 14-23, 2020, in the United States. CDC has issued updated interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States (4) and interim considerations for preparing for the potential management of anaphylaxis (5). In addition to screening for contraindications and precautions before administering COVID-19 vaccines, vaccine locations should have the necessary supplies available to manage anaphylaxis, should implement postvaccination observation periods, and should immediately treat persons experiencing anaphylaxis signs and symptoms with intramuscular injection of epinephrine (4,5).

Tenforde, M. W., et al. (2021). "Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged >/=65 Years - United States, January-March 2021." MMWR Morb Mortal Wkly Rep **70**(18): 674-679.

Adults aged >/=65 years are at increased risk for severe outcomes from COVID-19 and were identified as a priority group to receive the first COVID-19 vaccines approved for use under an Emergency Use Authorization (EUA) in the United States (1-3). In an evaluation at 24 hospitals in 14 states,* the effectiveness of partial or full vaccination(dagger) with Pfizer-BioNTech or Moderna vaccines against COVID-19-associated hospitalization was assessed among adults aged >/=65 years. Among 417 hospitalized adults aged >/=65 years (including 187 case-patients and 230 controls), the median age was 73 years, 48% were female, 73% were non-Hispanic White, 17% were non-Hispanic Black, 6% were Hispanic, and 4% lived in a long-term care facility. Adjusted vaccine effectiveness (VE) against COVID-19-associated hospitalization among adults aged >/=65 years was estimated to be 94% (95% confidence interval [CI] = 49%-99%) for full vaccination and 64% (95% CI = 28%-82%) for partial vaccination. These findings are consistent with efficacy determined from clinical trials in the subgroup of adults aged >/=65 years (4,5). This multisite U.S. evaluation under real-world conditions suggests that vaccination provided protection against COVID-19-associated hospitalization among adults aged >/=65 years. Vaccination is a critical tool for reducing severe COVID-19 in groups at high risk.

Teo, S. P. (2021). "Review of COVID-19 mRNA Vaccines: BNT162b2 and mRNA-1273." J Pharm Pract: 8971900211009650.

The United States Food and Drug Administration recently issued emergency use authorization for 2 mRNA vaccines for preventing COVID-19 disease caused by SARS-CoV-2 virus infections. BNT162b2 from Pfizer-BioNTech and mRNA-1273 by Moderna are planned for use in mass-immunization programs to curb the pandemic. A brief overview of COVID-19 mRNA vaccines is provided, describing the SARS-CoV-2 RNA, how mRNA vaccines work and the advantages of mRNA over other vaccine platforms. The Pfizer-BioNTech collaboration journey to short-list mRNA vaccine candidates and finally selecting BNT162b2 based on safety data is outlined, followed by the Phase 3 study of BNT162b2 demonstrating 95% efficacy in preventing COVID-19 infections. Studies regarding mRNA-1273 (Moderna) are described, including extended immunogenicity data up to 119 days. The Phase 3 COVE study of mRNA-1273 eventually showed vaccine efficacy of 94.5%. Recommendations for future mRNA vaccine

development are provided, including ongoing safety surveillance, evaluation in under-represented groups in previous studies and improving mRNA vaccine thermostability. Finally, further logistical considerations are required for manufacturing, storing, distribution and implementing mass vaccination programs to curb the pandemic.

Teo, S. P. (2021). "Review of COVID-19 Vaccines and Their Evidence in Older Adults." Ann Geriatr Med Res **25**(1): 4-9.

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic and significant loss of life. Older people are vulnerable to SARS-CoV-2 infections and complications; thus, they are a priority group to receive COVID-19 vaccines. This review discusses considerations for COVID-19 vaccines for older adults. The general concepts of vaccine effectiveness in older adults are described, particularly immune senescence and vaccine development approaches to improve immunogenicity. The types of COVID-19 vaccine platforms are also described before reviewing the available, although limited, evidence from phase 3 COVID-19 vaccine trials relevant to older adults. The BNT162b2 vaccine by Pfizer-BioNTech and mRNA-1273 vaccine from Moderna demonstrated high efficacy and immunogenicity, which were also observed in older people. While the ChAdOx1 nCoV-19 vaccine (AZD1222) by AstraZeneca demonstrated some efficacy in older people, the vaccine dose requires clarification through further studies. Finally, the Ad26.COV2.S vaccine by Janssen Pharmaceuticals shows promise as a single-dose vaccine with a potential durability of response.

Tsiambas, E., et al. (2021). "Impact of Ribosome Activity on SARS-CoV-2 LNP - Based mRNA Vaccines." Front Mol Biosci **8**: 654866.

Coronavirus-related Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) initially was detected in Wuhan, Hubei, China. Since early 2021, World Health Organization (WHO) has declared Coronavirus Disease 2019 (COVID-19) a pandemic due to rapidly transformed to a globally massive catastrophic viral infection. In order to confront this emergency situation, many pharmaceutical companies focused on the design and development of efficient vaccines that are considered necessary for providing a level of normalization in totally affected human social-economical activity worldwide. A variety of vaccine types are under development, validation or even some of them have already completed these stages, initially approved as conditional marketing authorisation by Food and Drug Administration (FDA), European Medicines Agency (EMA), and other national health authorities for commercial purposes (in vivo use in general population), accelerating their production and distribution process. Innovative nucleoside-modified viral messenger RNA (v-mRNA)-based vaccines encapsulated within nanoparticles-specifically lipid ones (LNPs)-are now well recognized. Although this is a promising genetic engineering topic in the field of nanopharmacogenomics or targeted nucleic vaccines, there are limited but continuously enriched in vivo data in depth of time regarding their safety, efficacy, and immune response. In the current paper we expand the limited published data in the field of ribosome machinery and SARS-CoV-2 mRNA fragment vaccines interaction by describing their functional specialization and modifications. Additionally, alterations in post-transcriptional/translational molecules and mechanisms that could potentially affect the interaction between target cells and vaccines are also presented. Understanding these mechanisms is a crucial step for the next generation v-mRNA vaccines development.

Tumban, E. (2020). "Lead SARS-CoV-2 Candidate Vaccines: Expectations from Phase III Trials and Recommendations Post-Vaccine Approval." Viruses **13**(1).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted primarily through respiratory droplets/aerosols and it causes COVID-19. The virus infects epithelial cells by using the spike protein on its surface to bind to angiotensin-converting enzyme 2 receptor on the cells. Thus, candidate vaccines targeting the spike protein are currently being developed to prevent against infections. Approximately 44 SARS-CoV-2 candidate vaccines are in clinical trials (phase I-III) and an additional 164 candidates are in preclinical stages. The efficacy data from phase I/II trials of lead candidate vaccines look very promising with virus-neutralizing geometric mean antibody titers in the range of 16.6-3906. Most recently, two SARS-CoV-2 candidate vaccines, BNT162b2 and mRNA-1273, have been granted the first emergency use authorization (EUA) in the U.S.; BNT162b2 has also been granted an EUA in the United Kingdom, Canada, and in the European Union. This review assesses whether SARS-CoV-2 candidate vaccines (with approved EUA or in phase III trials) meet the criteria for an ideal SARS-CoV-2 vaccine. The review concludes with expectations from phase III trials and recommendations for phase IV studies (post-vaccine approval).

Ura, T., et al. (2021). "New vaccine production platforms used in developing SARS-CoV-2 vaccine candidates." Vaccine **39**(2): 197-201.

The threat of the current coronavirus disease

pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is accelerating the development of potential vaccines. Candidate vaccines have been generated using existing technologies that have been applied for developing vaccines against other infectious diseases. Two new types of platforms, mRNA- and viral vector-based vaccines, have been gaining attention owing to the rapid advancement in their methodologies. In clinical trials, setting appropriate immunological endpoints plays a key role in evaluating the efficacy and safety of candidate vaccines. Updated information about immunological features from individuals who have or have not been exposed to SARS-CoV-2 continues to guide effective vaccine development strategies. This review highlights key strategies for generating candidate SARS-CoV-2 vaccines and considerations for vaccine development and clinical trials.

Urbina, F., et al. (2020). "Enzymatic Protein Biopolymers as a Tool to Synthetize Eukaryotic Messenger Ribonucleic Acid (mRNA) with Uses in Vaccination, Immunotherapy and Nanotechnology." Polymers (Basel) **12**(8).

Multi-subunit enzymes are protein biopolymers that are involved in many cellular processes. The enzyme that carries out the process of transcription of mRNAs is RNA polymerase II (RNAPII), which is a multi-subunit enzyme in eukaryotes. This protein biopolymer starts the transcription from specific sites and is positioned by transcription factors, which form a preinitiation complex (PIC) on gene promoters. To recognize and position the RNAPII and the transcription factors on the gene promoters are needed specific DNA sequences in the gene promoters, which are named promoter elements. Those gene promoter elements can vary and therefore several kinds of promoters exist, however, it appears that all promoters can use a similar pathway for PIC formation. Those pathways are discussed in this review. The in vitro transcribed mRNA can be used as vaccines to fight infectious diseases, e.g., in immunotherapy against cancer and in nanotechnology to deliver mRNA for a missing protein into the cell. We have outlined a procedure to produce an mRNA vaccine against the SARS-CoV-2 virus, which is the causing agent of the big pandemic, COVID-19, affecting human beings all over the world. The potential advantages of using eukaryotic RNAPII to synthetize large transcripts are outlined and discussed. In addition, we suggest a method to cap the mRNA at the 5' terminus by using enzymes, which might be more effective than cap analogs. Finally, we suggest the construction of a future multi-talented RNAPII, which would be able to synthetize large mRNA and cap them in the test tube.

Van Rostenberghe, H. (2021). "Primum Non Nocere." Malays J Med Sci **28**(1): 122-124.

The coronavirus disease 2019 (COVID-19) pandemic is severe and has not shown any signs of warning up to today. Biotech companies around the world have raced to come up with an acceptable vaccine and recently two mRNA vaccines have received emergency usage authorisation from regulatory bodies in several countries. mRNA vaccines, which consist of a new and revolutionary technology have not been previously tested widely on humans. Medium- and long-term safety data are not available. While many experts seem to support the start of a mass vaccination campaign, others feel there are too many unknowns to embark on a mass vaccination campaign. Concerns include uncertainties about the long-term effects of foreign mRNA on human cellular physiology and the possibility of vaccine-enhanced disease severity, which may not be unlikely with the current disease presentation of COVID-19.

Vasileiou, E., et al. (2021). "Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study." Lancet **397**(10285): 1646-1657.

BACKGROUND: The BNT162b2 mRNA (Pfizer-BioNTech) and ChAdOx1 nCoV-19 (Oxford-AstraZeneca) COVID-19 vaccines have shown high efficacy against disease in phase 3 clinical trials and are now being used in national vaccination programmes in the UK and several other countries. Studying the real-world effects of these vaccines is an urgent requirement. The aim of our study was to investigate the association between the mass roll-out of the first doses of these COVID-19 vaccines and hospital admissions for COVID-19. METHODS: We did a prospective cohort study using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19-EAVE II-database comprising linked vaccination, primary care, real-time reverse transcription-PCR testing, and hospital admission patient records for 5.4 million people in Scotland (about 99% of the population) registered at 940 general practices. Individuals who had previously tested positive were excluded from the analysis. A time-dependent Cox model and Poisson regression models with inverse propensity weights were fitted to estimate effectiveness against COVID-19 hospital admission (defined as 1-adjusted rate ratio) following the first dose of vaccine. FINDINGS: Between Dec 8, 2020, and Feb 22, 2021, a total of 1 331 993 people were vaccinated over the study period. The mean age of those vaccinated was 65.0 years (SD 16.2). The first dose of the BNT162b2 mRNA vaccine was associated with a vaccine effect of 91% (95% CI

85-94) for reduced COVID-19 hospital admission at 28-34 days post-vaccination. Vaccine effect at the same time interval for the ChAdOx1 vaccine was 88% (95% CI 75-94). Results of combined vaccine effects against hospital admission due to COVID-19 were similar when restricting the analysis to those aged 80 years and older (83%, 95% CI 72-89 at 28-34 days post-vaccination). INTERPRETATION: Mass roll-out of the first doses of the BNT162b2 mRNA and ChAdOx1 vaccines was associated with substantial reductions in the risk of hospital admission due to COVID-19 in Scotland. There remains the possibility that some of the observed effects might have been due to residual confounding. FUNDING: UK Research and Innovation (Medical Research Council), Research and Innovation Industrial Strategy Challenge Fund, Health Data Research UK.

Verbeke, R., et al. (2021). "The dawn of mRNA vaccines: The COVID-19 case." J Control Release **333**: 511-520.

In less than one year since the outbreak of the COVID-19 pandemic, two mRNA-based vaccines, BNT162b2 and mRNA-1273, were granted the first historic authorization for emergency use, while another mRNA vaccine, CVnCoV, progressed to phase 3 clinical testing. The COVID-19 mRNA vaccines represent a new class of vaccine products, which consist of synthetic mRNA strands encoding the SARS-CoV-2 Spike glycoprotein, packaged in lipid nanoparticles to deliver mRNA to cells. This review digs deeper into the scientific breakthroughs of the last decades that laid the foundations for the rapid rise of mRNA vaccines during the COVID-19 pandemic. As well as providing momentum for mRNA vaccines, SARS-CoV-2 represents an ideal case study allowing to compare design-activity differences between the different mRNA vaccine candidates. Therefore, a detailed overview of the composition and (pre)clinical performance of the three most advanced mRNA vaccines is provided and the influence of choices in their structural design on to their immunogenicity and reactogenicity profile is discussed in depth. In addition to the new fundamental insights in the mRNA vaccines' mode of action highlighted here, we also point out which unknowns remain that require further investigation and possibly, optimization in future mRNA vaccine development.

Wang, C., et al. (2021). "SARS-CoV-2 (COVID-19) vaccination in dermatology patients on immunomodulatory and biologic agents: Recommendations from the Australasian Medical Dermatology Group." Australas J Dermatol.

As the phase III COVID-19 vaccine trials excluded patients on immunosuppressive treatments, or patients with significant autoimmunity, the Australasian Medical Dermatology Group make the following preliminary recommendations around COVID-19 vaccination in dermatology patients on immunomodulatory and/or biologic agents. Vaccination against COVID-19 is strongly encouraged for all patients on immunomodulatory drugs and/or biologic agents. There are currently insufficient data to recommend one COVID-19 vaccine or vaccine type (mRNA, recombinant, inactivated virus) over another. No specific additional risk in patients on immunomodulatory or biologic therapies has so far been identified. Data on vaccine efficacy in patients on immunomodulatory or biologic therapies are missing, so standard vaccination protocols are recommended until otherwise advised.

Wang, F., et al. (2020). "An Evidence Based Perspective on mRNA-SARS-CoV-2 Vaccine Development." Med Sci Monit **26**: e924700.

The first outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, Hubei Province, China, in late 2019. The subsequent COVID-19 pandemic rapidly affected the health and economy of the world. The global approach to the pandemic was to isolate populations to reduce the spread of this deadly virus while vaccines began to be developed. In March 2020, the first phase I clinical trial of a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine, mRNA-1273, which encodes the spike protein (S protein) of SARS-CoV-2, began in the United States (US). The production of mRNA-based vaccines is a promising recent development in the production of vaccines. However, there remain significant challenges in the development and testing of vaccines as rapidly as possible to control COVID-19, which requires international collaboration. This review aims to describe the background to the rationale for the development of mRNA-based SARS-CoV-2 vaccines and the current status of the mRNA-1273 vaccine.

Wang, J. Y., et al. (2021). "An Autoantigen-ome from HS-Sultan B-Lymphoblasts Offers a Molecular Map for Investigating Autoimmune Sequelae of COVID-19." bioRxiv.

To understand how COVID-19 may induce autoimmune diseases, we have been compiling an atlas of COVID-autoantigens (autoAgs). Using dermatan sulfate (DS) affinity enrichment of autoantigenic proteins extracted from HS-Sultan lymphoblasts, we identified 362 DS-affinity proteins, of which at least 201 (56%) are confirmed autoAgs. Comparison with available multi-omic COVID data shows that 315 (87%) of the 362 proteins are affected in SARS-CoV-2 infection via altered expression, interaction with viral

components, or modification by phosphorylation or ubiquitination, at least 186 (59%) of which are known autoAgs. These proteins are associated with gene expression, mRNA processing, mRNA splicing, translation, protein folding, vesicles, and chromosome organization. Numerous nuclear autoAgs were identified, including both classical ANAs and ENAs of systemic autoimmune diseases and unique autoAgs involved in the DNA replication fork, mitotic cell cycle, or telomerase maintenance. We also identified many uncommon autoAgs involved in nucleic acid and peptide biosynthesis and nucleocytoplasmic transport, such as aminoacyl-tRNA synthetases. In addition, this study found autoAgs that potentially interact with multiple SARS-CoV-2 Nsp and Orf components, including CCT/TriC chaperonin, insulin degrading enzyme, platelet-activating factor acetylhydrolase, and the ezrin-moesin-radixin family. Furthermore, B-cell-specific IgM-associated ER complex (including MBZ1, BiP, heat shock proteins, and protein disulfide-isomerases) is enriched by DS-affinity and up-regulated in B-cells of COVID-19 patients, and a similar IgH-associated ER complex was also identified in autoreactive pre-B1 cells in our previous study, which suggests a role of autoreactive B1 cells in COVID-19 that merits further investigation. In summary, this study demonstrates that virally infected cells are characterized by alterations of proteins with propensity to become autoAgs, thereby providing a possible explanation for infection-induced autoimmunity. The COVID autoantigen-ome provides a valuable molecular resource and map for investigation of COVID-related autoimmune sequelae and considerations for vaccine design.

Wang, P., et al. (2021). "Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7." Nature **593**(7857): 130-135.

The COVID-19 pandemic has had widespread effects across the globe, and its causative agent, SARS-CoV-2, continues to spread. Effective interventions need to be developed to end this pandemic. Single and combination therapies with monoclonal antibodies have received emergency use authorization(1-3), and more treatments are under development(4-7). Furthermore, multiple vaccine constructs have shown promise(8), including two that have an approximately 95% protective efficacy against COVID-19(9,10). However, these interventions were directed against the initial SARS-CoV-2 virus that emerged in 2019. The recent detection of SARS-CoV-2 variants B.1.1.7 in the UK(11) and B.1.351 in South Africa(12) is of concern because of their purported ease of transmission and extensive mutations in the spike protein. Here we show that B.1.1.7 is refractory to neutralization by most monoclonal antibodies against the N-terminal domain of the spike protein and is relatively resistant to a few monoclonal antibodies against the receptor-binding domain. It is not more resistant to plasma from individuals who have recovered from COVID-19 or sera from individuals who have been vaccinated against SARS-CoV-2. The B.1.351 variant is not only refractory to neutralization by most monoclonal antibodies against the N-terminal domain but also by multiple individual monoclonal antibodies against the receptor-binding motif of the receptor-binding domain, which is mostly due to a mutation causing an E484K substitution. Moreover, compared to wild-type SARS-CoV-2, B.1.351 is markedly more resistant to neutralization by convalescent plasma (9.4-fold) and sera from individuals who have been vaccinated (10.3-12.4-fold). B.1.351 and emergent variants(13,14) with similar mutations in the spike protein present new challenges for monoclonal antibody therapies and threaten the protective efficacy of current vaccines.

Wang, R., et al. (2020). "Mutations on COVID-19 diagnostic targets." Genomics **112**(6): 5204-5213.

Effective, sensitive, and reliable diagnostic reagents are of paramount importance for combating the ongoing coronavirus disease 2019 (COVID-19) pandemic when there is neither a preventive vaccine nor a specific drug available for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It will cause a large number of false-positive and false-negative tests if currently used diagnostic reagents are undermined. Based on genotyping of 31,421 SARS-CoV-2 genome samples collected up to July 23, 2020, we reveal that essentially all of the current COVID-19 diagnostic targets have undergone mutations. We further show that SARS-CoV-2 has the most mutations on the targets of various nucleocapsid (N) gene primers and probes, which have been widely used around the world to diagnose COVID-19. To understand whether SARS-CoV-2 genes have mutated unevenly, we have computed the mutation rate and mutation h-index of all SARS-CoV-2 genes, indicating that the N gene is one of the most non-conservative genes in the SARS-CoV-2 genome. We show that due to human immune response induced APOBEC mRNA (C > T) editing, diagnostic targets should also be selected to avoid cytidines. Our findings might enable optimally selecting the conservative SARS-CoV-2 genes and proteins for the design and development of COVID-19 diagnostic reagents, prophylactic vaccines, and therapeutic medicines. AVAILABILITY: Interactive real-time online Mutation Tracker.

Watad, A., et al. (2021). "Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination." Vaccines (Basel) **9**(5).

BACKGROUND: Infectious diseases and vaccines can occasionally cause new-onset or flare of immune-mediated diseases (IMDs). The adjuvanticity of the available SARS-CoV-2 vaccines is based on either TLR-7/8 or TLR-9 agonism, which is distinct from previous vaccines and is a common pathogenic mechanism in IMDs. METHODS: We evaluated IMD flares or new disease onset within 28-days of SARS-CoV-2 vaccination at five large tertiary centres in countries with early vaccination adoption, three in Israel, one in UK, and one in USA. We assessed the pattern of disease expression in terms of autoimmune, autoinflammatory, or mixed disease phenotype and organ system affected. We also evaluated outcomes. FINDINGS: 27 cases included 17 flares and 10 new onset IMDs. 23/27 received the BNT - 162b2 vaccine, 2/27 the mRNA-1273 and 2/27 the ChAdOx1 vaccines. The mean age was 54.4 +/- 19.2 years and 55% of cases were female. Among the 27 cases, 21 (78%) had at least one underlying autoimmune/rheumatic disease prior the vaccination. Among those patients with a flare or activation, four episodes occurred after receiving the second-dose and in one patient they occurred both after the first and the second-dose. In those patients with a new onset disease, two occurred after the second-dose and in one patient occurred both after the first (new onset) and second-dose (flare). For either dose, IMDs occurred on average 4 days later. Of the cases, 20/27 (75%) were mild to moderate in severity. Over 80% of cases had excellent resolution of inflammatory features, mostly with the use of corticosteroid therapy. Other immune-mediated conditions included idiopathic pericarditis (n = 2), neurosarcoidosis with small fiber neuropathy (n = 1), demyelination (n = 1), and myasthenia gravis (n = 2). In 22 cases (81.5%), the insurgence of Adverse event following immunization (AEFI)/IMD could not be explained based on the drug received by the patient. In 23 cases (85.2%), AEFI development could not be explained based on the underlying disease/co-morbidities. Only in one case (3.7%), the timing window of the insurgence of the side effect was considered not compatible with the time from vaccine to flare. INTERPRETATION: Despite the high population exposure in the regions served by these centers, IMDs flares or onset temporally-associated with SARS-CoV-2 vaccination appear rare. Most are moderate in severity and responsive to therapy although some severe flares occurred. FUNDING: none.

Wayment-Steele, H. K., et al. (2020). "Theoretical basis for stabilizing messenger RNA through secondary structure design." bioRxiv.

RNA hydrolysis presents problems in manufacturing, long-term storage, world-wide delivery, and in vivo stability of messenger RNA (mRNA)-based vaccines and therapeutics. A largely unexplored strategy to reduce mRNA hydrolysis is to redesign RNAs to form double-stranded regions, which are protected from in-line cleavage and enzymatic degradation, while coding for the same proteins. The amount of stabilization that this strategy can deliver and the most effective algorithmic approach to achieve stabilization remain poorly understood. Motivated by the need for stabilized COVID-19 mRNA vaccines, we present simple calculations for estimating RNA stability against hydrolysis, and a model that links the average unpaired probability of an mRNA, or AUP, to its overall rate of hydrolysis. To characterize the stabilization achievable through structure design, we compare optimization of AUP by conventional mRNA design methods to results from the LinearDesign algorithm, a new Monte Carlo tree search algorithm called RiboTree, and crowdsourcing through the OpenVaccine challenge on the Eterna platform. Tests were carried out on mRNAs encoding nanoluciferase, green fluorescent protein, and COVID-19 mRNA vaccine candidates encoding SARS-CoV-2 epitopes, spike receptor binding domain, and full-length spike protein. We find that Eterna and RiboTree significantly lower AUP while maintaining a large diversity of sequence and structure features that correlate with translation, biophysical size, and immunogenicity. Our results suggest that increases in in vitro mRNA half-life by at least two-fold are immediately achievable and that further stability improvements may be enabled with thorough experimental characterization of RNA hydrolysis.

Wei, Y., et al. (2020). "Coronavirus genomes carry the signatures of their habitats." PLoS One **15**(12): e0244025.

Coronaviruses such as SARS-CoV-2 regularly infect host tissues that express antiviral proteins (AVPs) in abundance. Understanding how they evolve to adapt or evade host immune responses is important in the effort to control the spread of infection. Two AVPs that may shape viral genomes are the zinc finger antiviral protein (ZAP) and the apolipoprotein B mRNA editing enzyme-catalytic polypeptide-like 3 (APOBEC3). The former binds to CpG dinucleotides to facilitate the degradation of viral transcripts while the latter frequently deaminates C into U residues which could generate notable viral sequence variations. We tested the hypothesis that both APOBEC3 and ZAP impose selective pressures that shape the genome of an infecting coronavirus. Our investigation considered a comprehensive number of publicly available genomes for seven coronaviruses (SARS-CoV-2, SARS-CoV, and MERS infecting Homo sapiens, Bovine CoV infecting Bos taurus, MHV infecting Mus musculus, HEV infecting Sus scrofa, and CRCoV infecting Canis

lupus familiaris). We show that coronaviruses that regularly infect tissues with abundant AVPs have CpG-deficient and U-rich genomes; whereas those that do not infect tissues with abundant AVPs do not share these sequence hallmarks. Among the coronaviruses surveyed herein, CpG is most deficient in SARS-CoV-2 and a temporal analysis showed a marked increase in C to U mutations over four months of SARS-CoV-2 genome evolution. Furthermore, the preferred motifs in which these C to U mutations occur are the same as those subjected to APOBEC3 editing in HIV-1. These results suggest that both ZAP and APOBEC3 shape the SARS-CoV-2 genome: ZAP imposes a strong CpG avoidance, and APOBEC3 constantly edits C to U. Evolutionary pressures exerted by host immune systems onto viral genomes may motivate novel strategies for SARS-CoV-2 vaccine development.

Weissman, D., et al. (2021). "D614G Spike Mutation Increases SARS CoV-2 Susceptibility to Neutralization." Cell Host Microbe **29**(1): 23-31 e24.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein acquired a D614G mutation early in the pandemic that confers greater infectivity and is now the globally dominant form. To determine whether D614G might also mediate neutralization escape that could compromise vaccine efficacy, sera from spike-immunized mice, nonhuman primates, and humans were evaluated for neutralization of pseudoviruses bearing either D614 or G614 spike. In all cases, the G614 pseudovirus was moderately more susceptible to neutralization. The G614 pseudovirus also was more susceptible to neutralization by receptor-binding domain (RBD) monoclonal antibodies and convalescent sera from people infected with either form of the virus. Negative stain electron microscopy revealed a higher percentage of the 1-RBD "up" conformation in the G614 spike, suggesting increased epitope exposure as a mechanism of enhanced vulnerability to neutralization. Based on these findings, the D614G mutation is not expected to be an obstacle for current vaccine development.

Woldemeskel, B. A., et al. (2021). "SARS-CoV-2 mRNA vaccines induce broad CD4+ T cell responses that recognize SARS-CoV-2 variants and HCoV-NL63." J Clin Invest.

Recent studies have shown T cell cross-recognition of SARS-CoV-2 and common cold coronavirus spike proteins. However, the effect of SARS-CoV-2 vaccines on T cell responses to common cold coronaviruses remain unknown. In this study, we analyzed CD4+ T cell responses to spike peptides from SARS-CoV-2 and 3 common cold coronaviruses (HCoV-229E, HCoV-NL63, and HCoV-OC43) before and after study participants received Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) mRNA-based COVID-19 vaccines. Vaccine recipients made broad T cell responses to the SARS-CoV-2 spike protein and we identified 23 distinct targeted peptides in 9 participants including one peptide that was targeted by 6 individuals. Only 4 out of these 23 targeted peptides would potentially be affected by mutations in the UK (B.1.1.7) and South African (B.1.351) variants and CD4+ T cells from vaccine recipients recognized the 2 variant spike proteins as effectively as the spike protein from the ancestral virus. Interestingly, we saw a 3-fold increase in the CD4+ T cell responses to HCoV-NL63 spike peptides post-vaccination. Our results suggest that T cell responses elicited or enhanced by SARS-CoV-2 mRNA vaccines may be able to control SARS-CoV-2 variants and lead to cross-protection from some endemic coronaviruses.

Wu, K., et al. (2021). "Variant SARS-CoV-2 mRNA vaccines confer broad neutralization as primary or booster series in mice." bioRxiv.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of a global pandemic that has led to more than 2.8 million deaths worldwide. Safe and effective vaccines are now available, including Moderna's COVID-19 vaccine (mRNA-1273) that showed 94% efficacy in prevention of symptomatic COVID-19 disease in a phase 3 clinical study. mRNA-1273 encodes for a prefusion stabilized full length spike (S) protein of the Wuhan-Hu-1 isolate. However, the emergence of SARS-CoV-2 variants has led to concerns of viral escape from vaccine-induced immunity. Several emerging variants have shown decreased susceptibility to neutralization by vaccine induced immunity, most notably the B.1.351 variant, although the overall impact on vaccine efficacy remains to be determined. Here, we present the initial evaluation in mice of two updated COVID-19 mRNA vaccines designed to target emerging SARS-CoV-2 variants: (1) monovalent mRNA-1273.351 encodes for the S protein found in the B.1.351 lineage and (2) mRNA-1273.211 comprising a 1:1 mix of mRNA-1273 and mRNA-1273.351. Both vaccines were evaluated as a 2-dose primary series in mice; mRNA-1273.351 was also evaluated as a booster dose in animals previously vaccinated with 2-doses of mRNA-1273. The results demonstrated that a primary vaccination series of mRNA-1273.351 was effective at increasing neutralizing antibody titers against the B.1.351 lineage, while mRNA-1273.211 was most effective at providing broad cross-variant neutralization in mice. In addition, these results demonstrated a third dose of mRNA-1273.351 significantly increased both wild-type and B.1.351-specific neutralization titers. Both mRNA-1273.351 and mRNA-1273.211 are currently being evaluated in additional pre-clinical challenge models

and in phase 1/2 clinical studies.

Wu, Z. and T. Li (2021). "Nanoparticle-Mediated Cytoplasmic Delivery of Messenger RNA Vaccines: Challenges and Future Perspectives." Pharm Res **38**(3): 473-478.

The COVID-19 pandemic has left scientists and clinicians no choice but a race to find solutions to save lives while controlling the rapid spreading. Messenger RNA (mRNA)-based vaccines have become the front-runners because of their safety profiles, precise and reproducible immune response with more cost-effective and faster production than other types of vaccines. However, the physicochemical properties of naked mRNA necessitate innovative delivery technologies to ferry these 'messengers' to ribosomes inside cells by crossing various barriers and subsequently induce an immune response. Intracellular delivery followed by endosomal escape represents the key strategies for cytoplasmic delivery of mRNA vaccines to the target. This Perspective provides insights into how state-of-the-art nanotechnology helps break the delivery barriers and advance the development of mRNA vaccines. The challenges remaining and future perspectives are outlined.

Xia, X. (2021). "Domains and Functions of Spike Protein in Sars-Cov-2 in the Context of Vaccine Design." Viruses **13**(1).

The spike protein in SARS-CoV-2 (SARS-2-S) interacts with the human ACE2 receptor to gain entry into a cell to initiate infection. Both Pfizer/BioNTech's BNT162b2 and Moderna's mRNA-1273 vaccine candidates are based on stabilized mRNA encoding prefusion SARS-2-S that can be produced after the mRNA is delivered into the human cell and translated. SARS-2-S is cleaved into S1 and S2 subunits, with S1 serving the function of receptor-binding and S2 serving the function of membrane fusion. Here, I dissect in detail the various domains of SARS-2-S and their functions discovered through a variety of different experimental and theoretical approaches to build a foundation for a comprehensive mechanistic understanding of how SARS-2-S works to achieve its function of mediating cell entry and subsequent cell-to-cell transmission. The integration of structure and function of SARS-2-S in this review should enhance our understanding of the dynamic processes involving receptor binding, multiple cleavage events, membrane fusion, viral entry, as well as the emergence of new viral variants. I highlighted the relevance of structural domains and dynamics to vaccine development, and discussed reasons for the spike protein to be frequently featured in the conspiracy theory claiming that SARS-CoV-2 is artificially created.

Xie, L., et al. (2021). "SARS_CoV2 RBD gene transcription cannot be driven by CMV promoter." Virology **558**: 22-27.

Cytomegalovirus (CMV) promoter drives various gene expression and yields sufficient protein for further functional investigation. Receptor binding domain (RBD) on spike protein of the SARS_CoV2 is the most critical portal for virus infection. Thus native conformational RBD protein may facilitate biochemical identification of RBD and provide valuable support of drug and vaccine design for curing COVID-19. We attempted to express RBD under CMV promoter in vitro, but failed. RBD-specific mRNA cannot be detected in cell transfected with recombinant plasmids, in which CMV promoter governs the RBD transcription. Additionally, the pCMV-Tag2B-SARS_CoV2_RBD trans-inactivates CMV promoter transcription activity. Alternatively, we identified that both Chicken beta-actin promoter and Vaccinia virus-specific medium/late (M/L) promoter (pSYN) can highly precede SARS_CoV2 RBD expression. Our findings provided evidence that SARS_CoV2 RBD gene can be driven by Chicken beta-actin promoter or Vaccinia virus-specific medium/late promoter instead of CMV promoter, thus providing valuable information for RBD feature exploration.

Xie, X., et al. (2021). "Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera." bioRxiv.

Rapidly spreading variants of SARS-CoV-2 that have arisen in the United Kingdom and South Africa share the spike N501Y substitution, which is of particular concern because it is located in the viral receptor binding site for cell entry and increases binding to the receptor (angiotensin converting enzyme 2). We generated isogenic N501 and Y501 SARS-CoV-2. Sera of 20 participants in a previously reported trial of the mRNA-based COVID-19 vaccine BNT162b2 had equivalent neutralizing titers to the N501 and Y501 viruses.

Xu, G. and Y. Lu (2021). "COVID-19 mRNA Vaccination-Induced Lymphadenopathy Mimics Lymphoma Progression on FDG PET/CT." Clin Nucl Med **46**(4): 353-354.

ABSTRACT: We present here a 72-year-old man with mantle cell lymphoma who has completed chemotherapy and achieved complete metabolic response to the therapy 10 months ago. Series follow-up FDG PET/CT scans have been negative for lymphoma. Current FDG PET/CT scan showed a new cluster of subcentimeter left axillary lymphadenopathy with avid FDG uptake. There was also focal FDG uptake in the left upper arm deltoid muscle and adjacent subcutaneous soft tissue, with no other

abnormal FDG-avid lesion or suspicious CT image findings. The medical history revealed that the patient received COVID-19 mRNA vaccine 2 days before the FDG PET/CT examination.

Yarmarkovich, M., et al. (2020). "Identification of SARS-CoV-2 Vaccine Epitopes Predicted to Induce Long-Term Population-Scale Immunity." Cell Rep Med **1**(3): 100036.

Here we propose a SARS-CoV-2 vaccine design concept based on identification of highly conserved regions of the viral genome and newly acquired adaptations, both predicted to generate epitopes presented on major histocompatibility complex (MHC) class I and II across the vast majority of the population. We further prioritize genomic regions that generate highly dissimilar peptides from the human proteome and are also predicted to produce B cell epitopes. We propose sixty-five 33-mer peptide sequences, a subset of which can be tested using DNA or mRNA delivery strategies. These include peptides that are contained within evolutionarily divergent regions of the spike protein reported to increase infectivity through increased binding to the ACE2 receptor and within a newly evolved furin cleavage site thought to increase membrane fusion. Validation and implementation of this vaccine concept could specifically target specific vulnerabilities of SARS-CoV-2 and should engage a robust adaptive immune response in the vast majority of the population.

Yarmarkovich, M., et al. (2020). "A SARS-CoV-2 Vaccination Strategy Focused on Population-Scale Immunity." SSRN: 3575161.

Here we propose a vaccination strategy for SARS-CoV-2 based on identification of both highly conserved regions of the virus and newly acquired adaptations that are presented by MHC class I and II across the vast majority of the population, are highly dissimilar from the human proteome, and are predicted B cell epitopes. We present 65 peptide sequences that we expect to result in a safe and effective vaccine which can be rapidly tested in DNA, mRNA, or synthetic peptide constructs. These include epitopes that are contained within evolutionarily divergent regions of the spike protein reported to increase infectivity through increased binding to the ACE2 receptor, and within a novel furin cleavage site thought to increase membrane fusion. This vaccination strategy specifically targets unique vulnerabilities of SARS-CoV-2 and should engage a robust adaptive immune response in the vast majority of the human population. Funding: This work was supported by a St. Baldrick's-Stand Up To Cancer Pediatric Dream Team Translational Research Grant (SU2C-AACR-DT2727) and the Beau Biden Cancer Moonshot Pediatric Immunotherapy Discovery and Development Networ (NCI Grant U54 CA232568). Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research. This work was also supported by NIH R35 CA220500 and the Giulio D'Angio Endowed Chair and the Quod Erat Demonstrandum (QED) program at the Science Center in Philadelphia.

Zafar, S., et al. (2020). "COVID-19: Current Developments and Further Opportunities in Drug Delivery and Therapeutics." Pharmaceutics **12**(10).

SARS-CoV-2 has affected people from all age groups, races and ethnicities. Given that many infected individuals are asymptomatic, they transmit the disease to others unknowingly, which has resulted in the spread of infection at an alarming rate. This review aims to provide an overview of the pathophysiology, preventive measures to reduce the disease spread, therapies currently in use, an update on vaccine development and opportunities for vaccine delivery. The World Health Organization has advised several precautions including social distancing, hand washing and the use of PPE including gloves and face masks for minimizing the spread of SARS-CoV-2 infection. At present, several antiviral therapies previously approved for other infections are being repositioned to study their efficacy against SARS-CoV-2. In addition, some medicines (i.e., remdesivir, chloroquine, hydroxychloroquine) have received emergency use authorisation from the FDA. Plasma therapy has also been authorised for emergency use for the treatment of COVID-19 on a smaller scale. However, no vaccine has been approved so far against this virus. Nevertheless, several potential vaccine targets have been reported, and development of different types of vaccines including DNA, mRNA, viral vector, inactivated, subunit and vaccine-like particles is in process. It is concluded that a suitable candidate delivered through an advanced drug delivery approach would effectively boost the immune system against this coronavirus.

Zeng, C., et al. (2020). "Leveraging mRNA Sequences and Nanoparticles to Deliver SARS-CoV-2 Antigens In Vivo." Adv Mater **32**(40): e2004452.

SARS-CoV-2 has become a pandemic worldwide; therefore, an effective vaccine is urgently needed. Recently, messenger RNAs (mRNAs) have emerged as a promising platform for vaccination. In this work, the untranslated regions (UTRs) of mRNAs are systematically engineered in order to enhance protein production. Through a comprehensive analysis of endogenous gene expression and de novo design of UTRs, the optimal combination of 5' and 3' UTR are identified and termed NASAR, which are 5- to 10-fold

more efficient than the tested endogenous UTRs. More importantly, NASAR mRNAs delivered by lipid-derived TT3 nanoparticles trigger a dramatic expression of potential SARS-CoV-2 antigens. The antigen-specific antibodies induced by TT3-nanoparticles and NASAR mRNAs are over two orders of magnitude more than that induced by the FDA-approved lipid nanoparticle material MC3 in vaccinated mice. These NASAR mRNAs merit further development as alternative SARS-CoV-2 vaccines.

Zhang, C., et al. (2020). "Perspectives on development of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)." Hum Vaccin Immunother **16**(10): 2366-2369.

The recent outbreak of Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been characterized by the World Health Organization (WHO) as a controllable global pandemic. The spike (S) glycoprotein mediates binding to the angiotensin-converting enzyme 2 (ACE2) receptor for virus entry and also services as the target of virus-neutralizing antibodies, making it an attractive and leading viral antigen for vaccine development. No vaccine against any human coronavirus is available to date. In learning from the experience of developing Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV vaccine candidates in preclinical and clinical trials, the most promising strategies for SARS-CoV-2 vaccines should employ viral-vector platforms, properly adjuvanted recombinant protein or DNA/mRNA encoding an engineered sequence of trimeric S protein in pre-fusion conformation.

Zhou, P., et al. (2021). "Research progress and challenges to coronavirus vaccine development." J Med Virol **93**(2): 741-754.

Coronaviruses (CoVs) are nonsegmented, single-stranded, positive-sense RNA viruses highly pathogenic to humans. Some CoVs are known to cause respiratory and intestinal diseases, posing a threat to the global public health. Against this backdrop, it is of critical importance to develop safe and effective vaccines against these CoVs. This review discusses human vaccine candidates in any stage of development and explores the viral characteristics, molecular epidemiology, and immunology associated with CoV vaccine development. At present, there are many obstacles and challenges to vaccine research and development, including the lack of knowledge about virus transmission, pathogenesis, and immune response, absence of the most appropriate animal models.

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