Review Article

Unlocking the Potentials of COVID-19 Vaccines, ~~plasma~~ Plasma ~~convalescence~~ Convalescence in the Management of SARS-COV-2 Coronavirus P~~p~~andemic~~.~~

ABSTRACT

The coronavirus vaccine (COVID-19 vaccines have been developed to provide an acquired immunity against the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the causal agent of coronavirus infection Prior to the outbreak of the pandemic, scientific knowledge on the structure and function of the virus was known and well established together with other virus causing diseases such the middle East respiratory syndrome (MERS). The un-predicted global health disaster caused by COVID-19 led to the urgent need for the vaccine discovery and development by different research groups since 2019. Currently with the approval of several vaccines by the FDA, we are motivated in to explore a comprehensive insight into the vaccine discovery and development process, the potential adverse event, and convalescence plasma therapy approach in the management of the global COVID-19 pandemic.

Key words, coronavirus, COVID-19, vaccine, SARS-COV-2, MERS, immunity, China, FDA, convalescence plasma therapy.

Comment [HA1]: Check it

INTRODUCTION.

On 10 January 2020, the SARS-CoV-2 genetic sequence data was shared through the genomic platform (GISAID), and by 19 March 2020, the global pharmaceutical industry declared a major commitment to address COVID-19 [1, 2]. Currently, in Phase III clinical trials, several COVID-19 vaccines have shown efficacy as high as 95% in preventing symptomatic COVID-19 infections [3]. As of March 2021, 12 vaccines were reported as authorized by at least one national regulatory authority for public use, that consist of two RNA vaccines, (Pfizer-BioNTech vaccine and the Moderna vaccine), some four conventional inactivated vaccines (BBIP-CorV, CoronaVac, Covaxin, and coviVac) [3, 4].

Four viral vector vaccines (Sputnik V, the Oxford-Astrazeneca vaccine, Convidicea and the Johnson and Johnson vaccine), and then two protein subunit vaccines (EpiVacCorona and RBD-Dimer) [4-6]. In total, as of March 2021, about 308 vaccine candidates were in various stages of development, with 73 in clinical research, including 24 in phase 1 trials, 33 in phase I-II trials, and 16 in Phase III development [6-9]. The COVID-19 vaccines have already been introduced in many countries. Some of the regulatory characteristics of a good vaccine before it can be delivered for use includes the following;

Comment [HA2]: Check it

- The vaccines must be proven safe and effective in large ~~multicentered~~multicenter study (phase III) clinical trials [10-13]. Some COVID-19 vaccine candidates have completed their phase III trials, and many other potential vaccines are being developed.
- Independent reviews of the efficacy and safety evidence is required for each vaccine candidate, including regulatory review and approval in the country where the vaccine is manufactured, before WHO considers a vaccine candidate for prequalification. Part of this process also involves the Global Advisory Committee on Vaccine Safety [11-13].
- In addition to review of the data for regulatory purposes, the evidence must also be reviewed for the purpose of policy recommendations on how the vaccines should be used.
- An external panel of experts convened by WHO, called the Strategic Advisory Group of Experts on Immunization (SAGE), analyzes the results from clinical trials, along with evidence on the

disease, age groups affected, risk factors for disease, programmatic use, and other information. SAGE then recommends whether and how the vaccines should be used.

- Officials in individual countries decide whether to approve the vaccines for national use and develop policies for how to use the vaccines in their country based on the WHO recommendations.
- The vaccines must be manufactured in large quantities, which is a major and unprecedented challenge all the while continuing to produce all the other important life-saving vaccines already in use.
- The final step, requires that all approved vaccines require distribution through a complex logistical process, with rigorous stock management and temperature control in the cold chain regulatory quality process) [14].

Comment [HA3]: ?

Many countries have put in place the implementation of 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 [15-17]. As of the 15 March 2021, 381.34 million doses of COVID-19 vaccine have been administered worldwide based on official reports from national health agencies [7,18]. AstraZeneca-Oxford anticipates producing 3 billion doses by 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 Convidicea 500 million doses in 2021 [18-22]. By December 2020, more than 10 billion vaccine doses had been preordered by countries [23], with about half of the doses purchased by developed countries which comprises just 14% of the world's population [9, 24].

Before the onset of COVID-19, a vaccine for an infectious disease had never been produced in less than several years [25], and no vaccine is in existence yet for preventing a coronavirus infection in humans [26]. However, vaccines have been developed against many pathogens caused by coronaviruses, including (as of 2003) the infectious bronchitis virus in avian, canine coronavirus, and the feline coronavirus [2, 27-29]. Earlier studies to develop vaccines for viruses in the family Coronaviridae that affect humans have been aimed at severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [6, 30]. Vaccines against SARS [31] and MERS [32] have been tested in non-human animals in preclinical studies [33].

Comment [HA4]: ?

Studies reported in 2005 and 2006, showed that the identification and development of novel vaccines and drugs for the treatment and management of SARS was a priority for governments and state institutions, public health sectors globally at that time [9, 34-36]. Since 2020, there is no cure or protective vaccine proven to be safe and effective against SARS in humans [3, 37]. There is no proven existence of vaccine against MERS [38]. In is noted that when MERS was prevalent, it was assumed and postulated that the existing SARS research may provide a useful template for developing vaccines and therapeutic solution against a MERS-CoV infection [39-41]. As of March 2020, there was just one (DNA based) MERS vaccine which completed the Phase I clinical trials in humans [42], and three others in progress, all belonging to the viral-vectored vaccines: two adenoviral-vectored (ChAdOx1-MERS, BVRS-GamVac) and one MVA- -vectored (MVA-MERS-S) [43].

Background history of the coronavirus vaccine:

After the coronavirus was isolated in December 2019 [22], its genetic sequence was published on 11 January 2020, provoking an urgent international response to prepare for an outbreak and Fastrack development of a preventive COVID-19 vaccine [3, 17, 33]. As from early 2020, vaccine development has been expedited via unprecedented collaboration in the multinational pharmaceutical industry and between governments [20]. In June 2020, tens of billions of dollars were available for investment by corporations, governments, international health organizations, and university research groups to develop dozens of vaccine candidates and prepare for global vaccination programs to immunize against

Comment [HA5]: Check it

COVID-19 infection [15, 27, 44]. According to the Coalition for Epidemic Preparedness Innovations (CEPI), the geographic distribution of COVID-19 vaccine development puts North American entities having about 40% of the activity compared to 30% in Asia and Australia, 26% in Europe, and a few projects in South America and Africa [3, 28, 41].

In February 2020, the WHO said it did not expect a vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative virus, to become available in less than 18 months [9]. The rapidly growing infection rate of COVID-19 worldwide during early 2020 called for international alliances and government efforts to urgently organize resources to make multiple vaccines on shortened timelines [25], with four vaccine candidates entering human evaluation in March 2020. National regulatory authorities have granted emergency use authorizations for twelve vaccines. Six of those have been approved for emergency or full use by at least one WHO-recognized stringent regulatory ~~authorities .~~authorities.

On 24 June 2020, China approved the CanSino vaccine for limited use in the military and two inactivated virus vaccines for emergency use in high-risk occupations [45]. On 11 August 2020, Russia announced the approval of its Sputnik V vaccine for emergency use, though one month later only small amounts of the vaccine had been distributed for use outside of the phase 3 trial [9, 46]. The Pfizer–BioNTech partnership submitted an EUA request to the FDA for the mRNA vaccine BNT162b2 (active ingredient lozinameran) on 20 November 2020 [33, 47]. On 2 December 2020, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) (MHRA) gave a temporary regulatory approval for the Pfizer-Biotech vaccine [48, 49], becoming the first country to approve this vaccine and the first country in the Western world to approve the use of any COVID-19 vaccine [50]. As of 21 December, many countries and the European Union [51] have authorized or approved the Pfizer–BioNTech COVID-19 vaccine. On 11 December 2020, the United States Food and Drug Administration (FDA) ~~apprved~~approved an Emergency Use Authorization (EUA) for the Pfizer–BioNTech COVID-19 vaccine [52] and a week later, they granted an EUA for mRNA-1273, the Moderna vaccine [53].

Comment [HA6]: ?

Comment [HA7]: ?

Potential evaluation of Vaccine efficacy:

The effectiveness of a new vaccine is defined by its efficacy during clinical trials process [14]. The efficacy is the risk of getting the disease by vaccinated participants in the trial compared with the risk of getting the disease by unvaccinated participants [13]. An efficacy of 0% means that the vaccine does not work (identical to placebo). An efficacy of 50% means that there are half as many cases of infection as in unvaccinated individuals [35]. It is not straightforward to compare the efficacies of the different vaccines due to the fact that the trials were run with different populations, geographic locations, and variants of the virus [23, 36]. In the case of COVID-19, a vaccine efficacy of 67% may be enough to slow the pandemic, but this take into consideration that the vaccine confers sterilizing immunity which is necessary to prevent transmission [16]. Vaccine efficacy is an indication of disease prevention, and a poor indicator of transmissibility of SARS-CoV-2 since asymptomatic people can be highly infectious [7, 13]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) established a cutoff of 50% as the efficacy required to approve a COVID-19 vaccine [1, 17] and aiming for a realistic population vaccination coverage rate of 75%, while depending on the actual basic reproduction number. The necessary effectiveness of a COVID-19 vaccine is expected to be at least 70% to prevent an epidemic and at least 80% to eradicate it without further barrier-imposed measures, such as social distancing [30]

In calculating efficacy, symptomatic COVID-19 is generally defined as having both a positive PCR test and at least one or two of defined lists of COVID-19 symptoms, even though there is variation in exact specification between trials [3]. The trial location can affect the reported efficacy as different countries have different incidence prevalence of SARS-COV-2 variants.

Types of COVID-19 Variants:

The emergence of a SARS-CoV-2 variant that is moderately or fully resistant to the antibody response elicited by the current generation of COVID-19 vaccines may require modification of the vaccines [36]. Clinical trials indicate that many vaccines developed for the initial strain have lower efficacy for some variants against symptomatic COVID-19 [5]. Since February 2021, the FDA believed that all FDA authorized vaccines remained effective in protecting against circulating strains of SARS-CoV-2 [34]. In

SARS-COV-2 variant B.1.1.7:

In December 2020, a new SARS-CoV variant B.1.1.7, was identified in the UK [4, 19] and early results of study suggested protection to the UK variant from the Pfizer and Moderna vaccines [11, 21, 35]. One study indicated that the Oxford-Astrazeneca vaccine had an efficacy of 42–89% against the B.1.1.7 variant, versus 71–91% against non-B.1.1.7 variants [9, 45]. Preliminary data from a clinical trial on NovaVax vaccine indicated that the vaccine was about 96% effective for symptoms against the original variant, approximately 86% against B.1.1.7, and, 60% against the "South African" B.1.351 variant [21, 28]

The 501.V2 variant:

Moderna launched a trial of a new vaccine to tackle the South African 501.V2 also known as B.1.351 [14, 37]. On 17 February 2021, Pfizer announced neutralization activity was reduced by two-thirds for the 501.V2 variant, while stating no claims about the efficacy of the vaccine in preventing illness for this variant could yet be made [42]

In January, Johnson & Johnson, which held trials for its Ad26.COV2. S vaccine in South Africa, reported the level of protection against moderate to severe COVID-19 infection was 72% in the United States and 57% in South Africa [41].

On 6 February 2021, the Financial Times reported that provisional trial data from a study undertaken by South Africa's University of the Witwatersrand in conjunction with the Oxford University demonstrated reduced efficacy of the Oxford-AstrazenecaCOVID-19 vaccine against the 501.V2 variant [23, 40]. The study showed that in a sample size of 2,000 volunteers the AZD1222 vaccine indicated only "minimal protection" in all but the most severe cases of COVID-19 [2, 7]. On 7 February 2021, the Minister for Health for South Africa suspended the planned deployment of around 1 million doses of the vaccine whilst they examine the data and await advice on how to proceed [9].

Vaccine formulation

As of September 2020, eleven of the vaccine candidates in clinical development use adjuvants to enhance immunogenicity [12]. An immunological adjuvant is a substance formulated with a vaccine to elevate the immune response to an antigen [42], such as the COVID-19 virus or influenza virus [8]. Specifically, an adjuvant may be used in formulating a COVID-19 vaccine candidate to boost its immunogenicity and efficacy to reduce or prevent COVID-19 infection in vaccinated individuals [45]. Adjuvants used in COVID-19 vaccine formulation may be particularly effective for technologies using the inactivated COVID-19 virus and recombinant protein-based or vector-based vaccines [19]. In some cases, aluminum salts, known as "alum", were the first adjuvant used for licensed vaccines, and are the adjuvant of choice in some 80% of ~~adjuvanted~~adjuvant vaccines [37]. The alum adjuvant initiates diverse molecular and cellular mechanisms to enhance immunogenicity, including release of proinflammatory cytokines [42]

Comment [HA8]: Check it

Planning and development of vaccines.

Since early 2020, vaccine development has been expedited via unprecedented collaboration in the multinational pharmaceutical industry and the governments in some cases [45]. By the statement of the Coalition for Epidemic Preparedness Innovations (CEPI), the geographical distribution of COVID-19 vaccine development gives the North American entities having about 40% of the activity when compared to 30% in Asia and Australia, 26% in Europe, and a few projects in South America and Africa [46-48].

Formatted: Indent: First line: 0.5"

Multiple regulatory steps along the entire development path are evaluated, including [13, 49]

- The safety looking at the level of acceptable toxicity of the vaccine.,
- vulnerable populations as main targets,
- priority for vaccine efficacy breakthroughs,
- emphasis on the duration of vaccination protection,
- develop special delivery systems (such as oral or nasal, rather than by injection),
- dose regimen implementation,
- importance on stability and storage characteristics (cold chain quality assurance),
- need for emergency use authorization before formal licensing is granted,
- Platform for optimal manufacturing for scaling to billions of doses, and
- The dissemination and rapid distribution access of the licensed vaccine.

~~dosing~~ Dosing trials to run simultaneously over months, and potentially compromising safety and quality assurance [6, 53, 54]. Looking at the case of the Chinese vaccine as a case study it was observed that the Chinese vaccine developers and the government Chinese Centre for Disease Control and Prevention began their mobilization research in January 2020 [55], and by March were following up many candidates on short timelines, with the objective to showcase Chine state of the art technology strength over the developed countries [57], and their intention was to reassure the Chinese population about the potential quality of the vaccine and to reassure the Chinese people about the quality of vaccines produced in China [58-60].

The rapid development and the urgent need to produce a vaccine for the COVID-19 pandemic have potential risk implication of adverse risks and failure rate of delivering a safe, effective vaccine [4, 61]. Furthermore, preclinical and clinical research at the universities has been hindered by physical distancing and closing of laboratories [21, 49, 62].

Vaccines development have to progress through several phases of clinical trials to evaluate for safety, immunogenicity, efficacy, dose range and drug interactions, adverse effects [11, 17, 63]. Vaccine developers have obligation to invest much resources internationally to source out enough participants for Phase II–III clinical trials when the virus has been proven to be a 'moving target' of changing transmission rate across and within countries, now forcing companies to compete for trial participants [64-66]. Clinical trial organizers have other challenges of having people in the population unwilling to be vaccinated due to *vaccine hesitancy* and not wanting to be *guinea pigs*, a vaccine very new in the market with no long history of safety yet [19, 68] or disbelieving the science of the vaccine technology and its ability to prevent infection [3, 69]. Even though, new vaccines are developed during the COVID-19 pandemic, licensure of COVID-19 vaccine candidates still require submission of a full dossier of information on the discovery, development and manufacturing quality [23, 70-71].

Vaccine development Challenges:

There have been several potential challenges with the development of COVID-19 vaccine. The urgent need to create a vaccine for COVID-19 has led to compressed schedules that shortened the standard vaccine development timeline, and in many cases combining clinical trial steps over months, a process that normally takes over 10 years in a typically conducted sequential studies [51, 52]. The timelines for the conduct of clinical research is a sequential process which requires many years of studies, now compressed for safety, efficacy, and quality.

COVID-19 Vaccine Organizations

Internationally, the Access to COVID-19 Tools Accelerator is a G20 and World Health Organization (WHO) initiative that was announced in April 2020 [46, 72]. It is a cross-discipline support structure to enable partners to share resources and knowledge. This comprises of four main actors, each coordinated by two to three collaborating partners: Vaccines known as 'COVAX', Diagnostics, Therapeutics, and Health Systems Connector [44, 61, 73]. The WHO's April 2020 research and development Blueprint for the novel Coronavirus documented a large international, multi-site, individually randomized controlled clinical trial to allow the progressive evaluation of the benefits and risks of each potential promising vaccine candidate within 3–6 months of it being made available for the trial [29, 74]. The WHO vaccine coalition is to prioritize which vaccines should go into Phase II and III clinical trials, and then determine to ~~harmonized~~harmonize Phase III protocols for all vaccines that have gone through the pivotal development stage [45, 75].

National governments in sourced countries have also been involved in vaccine development. For example, Canada announced funding for 96 research vaccine research projects at Canadian companies and universities, with plans to establish a "vaccine bank" that could be used if another coronavirus outbreak occurs [46, 76], and to empower clinical trials, develop manufacturing and supply chains for vaccines [3, 47, 76].China has also taken a step forward to provide low-rate loans to a vaccine developer through its central bank and has readily made land available for the company to build production plants [27, 77].

Three Chinese vaccine companies and research institutes are supported by the government for financing research, conducting clinical trials, and manufacturing [40]. Great Britain formed a COVID-19 vaccine task force in the month of April 2020 to stimulate local efforts for accelerated development of a vaccine through collaborations of industry, universities, and government agencies [14, 78]. It encompassed every phase of development from research to manufacturing [49]. In the United States also, the Biomedical Advanced Research and Development Authority (BARDA), a federal agency funding disease-fighting technology, announced funding mobilization investments to support American COVID-19 vaccine development and manufacture of the most promising candidates [27, 79].

Most pharmaceutical companies with track record of experience in vaccine development at large scale such as Johnson & Johnson, AstraZeneca, and GlaxoSmithKline (GSK), have formed alliances with biotech companies, governments, and universities to accelerate progression to an effective vaccine [41, 80].

THE FOUR MAIN TYPES OF COVID-19 VACCINE:~~.~~

There are four categories of vaccines in clinical trials are whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA) [5, 14, 81]. Some of them try to smuggle the antigen into the body, others use the body's own cells to make the viral antigen.

Whole Virus:

Many conventional vaccines use whole viruses to trigger an immune response. There are two main approaches. Live attenuated vaccines use a weakened form of the virus that can still replicate without causing illness [83]. Inactivated vaccines use viruses whose genetic material has been destroyed so they cannot replicate, but can still trigger an immune response. Both types use well-established technology and pathways for regulatory approval, but live attenuated ones may risk causing disease in people with weak immune system [1, 14, 33] and will often require careful cold storage, making their use more challenging in low-resource countries [84]. Inactivated virus vaccines can be given to people with compromised immune systems but might also need cold storage [17].

Protein subunit:

The subunit vaccines are known to use fragments of the pathogen like protein fragments to trigger an immune response by so doing minimizing the risk of adverse effects, but weaken the immune response [12, 85] and therefore will require adjuvants, to boost the immune response. A named example of the protein subunit vaccine is the hepatitis B vaccine.

Nucleic acid:

Nucleic acid vaccines use genetic material of either RNA or DNA to provide cells with the instructions to make the antigen. In the case of COVID-19, this is usually the viral spike protein [29]. Once this genetic material gets into human cells, it uses our cells' protein factories to make the antigen that will trigger an immune response [86]. The advantages of such vaccines are that they are cheap and easy. Since the antigen is produced inside our own cells and in large quantities, the immune reaction should be strong. A downside, however, is that so far, no DNA or RNA vaccines have been licensed for human use, which may cause more hurdles with regulatory approval. In addition, RNA vaccines need to be kept at ultra-cold temperatures, -70 ºC or lower, which could prove challenging for countries that don't have specialized cold storage equipment, particularly low- and middle-income countries.

Viral vector:

Viral vector vaccines also work by giving cells genetic instructions to produce antigens. But they differ from nucleic acid vaccines in that they use a harmless virus, different from the one the vaccine is targeting, to deliver these instructions into the cell [27]. One type of virus that has often been used as a vector is adenovirus, which causes the common cold. As with nucleic acid vaccines, our own cellular machinery is hijacked to produce the antigen from those instructions, in order to trigger an immune response. Viral vector vaccines can mimic natural viral infection and should therefore trigger a strong immune response. However, since there is a chance that many people may have already been exposed to the viruses being used as vectors, some may be immune to it, making the vaccine less effective [70]. The

three types of response: (1) RNA vaccine, (2) subunit vaccine, (3) viral vector vaccine are illustrated in figure 1.

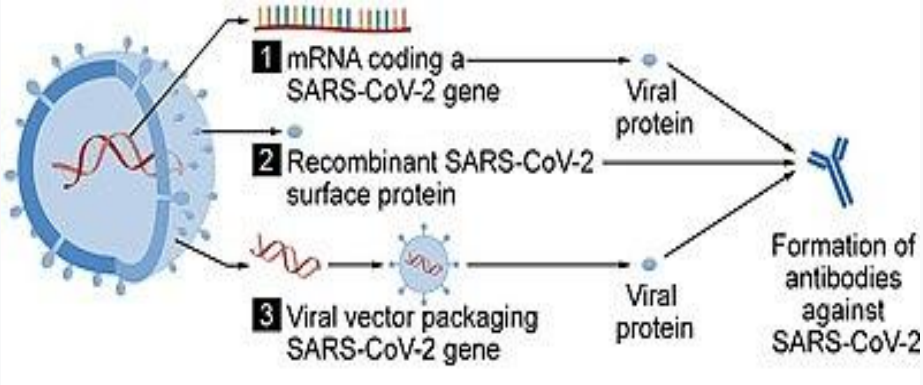

Figure 1:Conceptual diagram showing three vaccine types for forming SARS-CoV-2 proteins to prompt an immune response: (1) RNA vaccine, (2) subunit vaccine, (3) viral vector vaccine [82].

As of January 2021, nine different technology platforms– with the technology of numerous candidates remaining undefined – are under research and development to create an effective vaccine against COVID-19 [30]. Most of the platforms of vaccine candidates in clinical trials were focused on the coronavirus spike protein and its variants as the primary antigen of COVID-19 infection [60]. Platforms being developed in 2020 involved the nucleic acid technologies, (nucleoside-modified messenger RNA and DNA), non-replicating viral vectors, peptides, recombinant proteins, live attenuated viruses, and inactivated viruses [17, 45, 72].

Many vaccine technologies being developed for COVID-19 are not like vaccines already in use to prevent influenza, but rather are using "next-generation" strategies for precision on COVID-19 infection mechanisms [11]. Vaccine platforms in development may improve flexibility for antigen manipulation and effectiveness for targeting mechanisms of COVID-19 infection in susceptible population subgroups, such as healthcare workers, the elderly, children, pregnant women, and people with existing weakened immune systems [84]

RNA vaccines

An RNA vaccine contains RNA which, when introduced into a tissue, acts as messenger RNA (mRNA) to cause the cells to build the foreign protein and stimulate an adaptive immune response which teaches the body how to identify and destroy the corresponding pathogen or cancer cells [49]. RNA vaccines often, but not always, use nucleoside-modified messenger RNA. The delivery of mRNA is achieved by a coformulation of the molecule into lipid nanoparticles which protect the RNA strands and help their absorption into the cells [88]. RNA vaccines were the first COVID-19 vaccines to be authorized in the United States and the European Union [23, 86]. As of January 2021, authorized vaccines of this type are the Pfizer-BioNtech COVID-19 [90] and the Moderna COVID 19 vaccine [91]. As of February 2021, the CVnCoV RNA vaccine from CureVac is awaiting authorization in the EU [91, 92]. The illustration of the RNA vaccine Messenger RNA is demonstrated in Figure 2.

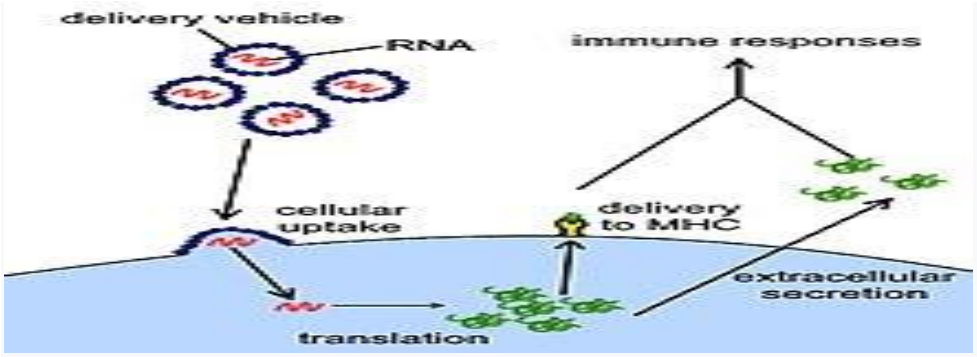

Figure2: Schematic illustration of the operation of an RNA vaccine. Messenger RNA contained in the vaccine enters cells and is translated into foreign proteins, which trigger an immune response [90].

Adenovirus vector vaccines

These vaccines are examples of non-replicating viral vectors, using an adenovirus shell containing DNA that encodes a SARS-CoV-2 protein [35, 93]. The viral vector-based vaccines against COVID-19 are non-replicating, meaning that they do not make new virus particles, but rather produce only the antigen which elicits a systemic immune response [17, 93]. As of January 2021, authorized vaccines of this type are the British Oxford–AstraZeneca COVID-19 vaccine [94], Russian Sputnik V [95], Chinese Convidicea, and the Johnson & Johnson COVID-19 vaccine [96]. Convidicia and Johnson & Johnson's vaccines are both one-shot vaccines which offer less complicated logistics; and can be stored under ordinary refrigeration for several months [97]. Sputnik V, uses Ad26 for the first dose the same as Johnson & Johnson's vaccine and Ad5 for the 2nd dose the same as Convidicia with similar single dose effectiveness and full trial taking place on single dose effectiveness.

Inactivated virus vaccines:

Inactivated vaccines consist of virus particles that have been grown in culture and then are killed using a method such as heat or formaldehyde to lose disease producing capacity, while still stimulating an immune response [25]. As of January 2021, authorized vaccines of this type are the Chinese CoronaVac [97], BBIBP-CorV [98] and the Indian Covaxin, as well as CoviVac [99]. Vaccines in clinical trials include the Valneva COVID-19 vaccine [78, 100].

Subunit vaccines:

Subunit vaccines present one or more antigens without introducing whole pathogen particles. The antigens involved are often protein subunits, but can be any molecule that is a fragment of the pathogen [101]

As of January 2021, the only authorized vaccine of this type was the peptide vaccine EpiVacCorona [23, 102]. Vaccines in clinical trials include the Novavax COVID-19 vaccine [12, 44] and RBD-Dimer [3, 103]. The V451 vaccine was previously in clinical trials, which were terminated because it was found that the vaccine could potentially cause incorrect results for subsequent HIV testing [67, 85]

Other types

Additional types of vaccines that are in clinical trials include multiple DNA plasmid vaccines [94, 98] at least two lentivirus vector vaccines [98] a conjugate vaccine, and a vesicular stomatitis virus displaying the SARS-CoV-2 spike protein [99]. Scientists investigated whether existing vaccines for unrelated conditions could prime the immune system and lessen the severity of COVID-19 infection [83]. There is experimental evidence that the BCG vaccine for tuberculosis has non-specific effects on the immune system, but no evidence that this vaccine is effective against COVID-19 [29].

Overview of the Vaccine approach for the management of COVID19 pandemic:

Post-vaccination embolic and thrombotic clinical adverse events

Post-vaccination embolic and thrombotic events, also termed vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) [101] or vaccine-induced immune thrombotic thrombocytopenia (VITT)[102, 103] are rare types of blood clotting events that were initially observed in a very small number of people who had previously received the Oxford–AstraZeneca COVID-19 vaccine (AZD1222) during the COVID-19 pandemic [101, 104]. It was subsequently also described in the Johnson & Johnson COVID-19 vaccine [108], leading to suspension of its use until its safety had been reassessed [105-107].

In April 2021, AstraZeneca and the EMA updated their information for healthcare professionals about AZD1222, saying it was "considered plausible" that there was a causal relationship between the vaccination and the occurrence of thrombosis in combination with thrombocytopenia and that, "although such adverse reactions are very rare, they exceeded what would be expected in the general population [105, 106]. Guidelines from professional societies recommend treatment with alternative anticoagulants instead of heparin, as there is a possibility that it may aggravate the phenomenon [100]

Signs and symptoms:

Thrombosis

Formatted: Font: Bold

Formatted: Indent: First line: 0.5"

The thrombosis events associated with the COVID-19 vaccine may occur 5-28 days after its administration. Several relatively unusual types of thrombosis has been specifically reported to occur in those with the reaction [109]: There has been cerebral venous sinus thrombosis and thrombosis of the splanchnic veins. Cerebral venous sinus thrombosis may cause severe headache, stroke-like symptoms (weakness of a limb and/or facial muscles), seizures and coma [15, 107], while the Splanchnic vein thrombosis may cause abdominal pain accumulation of fluid in the abdominal cavity and gastro intestinal bleeding [107, 110].

Other forms of thrombosis, such as the more common pulmonary embolism, may also occur. Arterial thrombosis has also been reported [108]. The low platelet count may manifest as tiny blood spots under the skin beyond the site of the injection [108]. Disseminated intravascular coagulation (DIC)., diffuse formation of blood clots throughout the blood vessels of the body, has been reported as part of the syndrome [109]. DIC may cause a range of symptoms, including abnormal bleeding, breathlessness, chest pain, neurological symptoms, low blood pressure, or swelling [21, 110]. COVID-19 vaccines have some adverse effects that are listed as common in the two- or three-days following vaccination which are usually mild and temporary [19]. The rare simultaneous occurrence of thrombocytopenia (low blood platelets) with blood clots after vaccination raised the original concern about this condition [47, 111]. In many cases where acute thrombosis and thrombocytopenia have been found together after COVID-19

vaccination, an antibody against platelet factor has been identified [22, 112]. This phenomenon is mostly encountered in some people who have been administered heparin, but none of the reported cases had received heparin [24]. More rarely, this phenomenon had previously been described as an autoimmune phenomenon in people who had not been exposed to heparin [19, 57, 113]. One striking feature of thrombocytopenia in the presence of anti-PF4 antibodies is the propensity of some to develop thrombosis, a phenomenon called heparin-induced thrombocytopenia if heparin is involved [30, 114]

Thrombocytopenia is generally a common symptom after or during many viral infections [9] and it "has been consistently reported" after administration of adenoviral gene transfer vectors [11, 66, 115], although its mechanisms are not yet known. There is no confirmed causal link to the syndrome and any COVID-19 vaccination [45]. However, EMA is conducting investigations into AZD1222 and the Johnson and Johnson COVID-19 (Janssen) vaccine (J&J) for possible causal links [88]. On 7 April 2021 the EMA noted one "plausible explanation" for the combination of blood clots and low blood platelets is "an immune response, leading to a condition similar to the one seen sometimes in patients treated with heparin", that is heparin induced thrombocytopenia (HIT) [109].

CONVALESCENCE PLASMA THERAPY APPROACH:

Convalescent plasma generated great enthusiasm in the earliest days of the coronavirus disease 2019 (covid-19) pandemic because of a plausible mechanism of action, its 100-year history of use in the treatment of other infectious diseases, and rapid availability from voluntary donors [111]. In the linked PLACID Trial, Agarwal and colleagues evaluated convalescent plasma for the treatment of moderate covid-19 in patients admitted to hospital in India [107, 112]. Strengths of the study included a primary "hard" outcome meaningful to patients, "real world" patient enrollment with no exclusions for comorbidities, careful attention to donor selection and safety screening of donated plasma, post facto quantitative testing of antibody titers in all plasma samples, assessment of secondary patient outcomes, and evaluation of the efficacy of the subsample of plasma donations that contained detectable titers of antibodies to severe acute respiratory coronavirus 2 (SARS-CoV-2), the virus responsible for covid-19 [32, 115].

In prespecified, intention-to-treat analyses, the PLACID Trial investigators found no net benefit associated with convalescent plasma in patients admitted to hospital with moderate covid-19 [116, 117]. The composite primary outcome (progression to severe disease or all-cause mortality at 28 days) occurred in 19% (44/235) of patients in the intervention arm and 18% (41/229) of patients in the control arm (risk ratio 1.04, 95% confidence interval 0.71 to 1.54) [107, 118]. Restricting the comparison to the subset of patients who received plasma with detectable antibody titers did not change the outcome. The primary hypothesized mechanism of benefit from convalescent plasma is through direct antiviral action of neutralizing antibodies on SARS-CoV-2 RNA [105, 118] In the PLACID Trial, a statistically significant 20% higher rateofconversiontoanegativeresultforSARS-CoV-2 RNA occurred on day 7 among patients in the intervention arm.

The most common use of therapeutic plasma, which contains more than 1000 different proteins, is for the management of acute bleeding and complex coagulopathies [5, 106, 119]. Despite the presence in plasma of anticoagulation factors such as antithrombin and protein C, the net effect of plasma is prothrombotic. Immunoglobulin therapy, which is derived from whole plasma, is subject to a US Food and Drug Administration warning about the risks of thrombosis, particularly in older patients, those with cardiovascular risk factors, and those with hypercoagulable conditions [108]. It is now widely recognized

that covid-19 is a life-threatening thrombotic disorder. An excellent recent pathophysiology synthesis concluded that "SARS-CoV-2notonlyproducesaninflammatoryand hypercoagulable state, but also a hypofibrinolytic state not seen with most other types of coagulopathy [108]. Most recently, plasma from convalescent covid-19 patients has been shown to directly cause endothelial cell damage *in vitro*.

The PLACID Trial was a rigorous randomized controlled study on a topic of enormous global importance, ethically designed and implemented given the contemporaneous state of scientific knowledge about SARS-CoV-2.4 With publication of the findings, the bar has been raised for all ongoing and future trials [105].

Principles of targeting cells' 'trash compactor' as a potential lead to a new potential antiviral approach to fight COVID-19 infection and management.

COVID-19 is an emerging, rapidly evolving situation and the National Institute of Health (NIH) scientists have discovered a key pathway in lysosomes that coronaviruses use to exit cells. The principles of Targeting cells' 'trash compactor' could lead to a new potential antiviral approach to fight COVID-19 infection and management [29, 32, 120]. A biological pathway has been elucidated that the novel coronavirus appears to use to hijack and exit cells as it spreads through the body. A better understanding of this important pathway may provide vital insight in stopping the transmission of the SARS-CoV-2 virus the causal agent of COVID-19 disease [88, 121].

In cell studies, the researchers reported for the first time that the coronavirus can exit infected cells through the lysosome, which is an organelle known as the cells' "trash compactor." Naturally, the lysosome is conditioned to destroy viruses and other pathogens before they leave the cells. However, the researchers out found that the coronavirus deactivates the lysosome's disease-fighting mechanism, permitting the virus it to freely spread throughout the body [14, 39, 122]. Strategy to target this lysosomal pathway could lead to the development of new, more effective antiviral therapies to fight COVID-19. The findings is a new hope and come at a time when new coronavirus cases are surging worldwide, with related U.S. deaths nearing 225,000 [41, 123].

Scientists have known for some time that viruses enter and infect cells and then use the cell's protein-making machinery to make multiple copies of themselves before escaping the cell. However, researchers have only a limited understanding of exactly how viruses exit cells. An illustration on how the virus exit the cells through lysosomes is shown in figure 4.
Illustration shows components of the lysosome exocytosis pathway, which coronaviruses use to exit cells. Also shown are components of the normal biosynthetic secretory pathway.

Formatted: Not Highlight

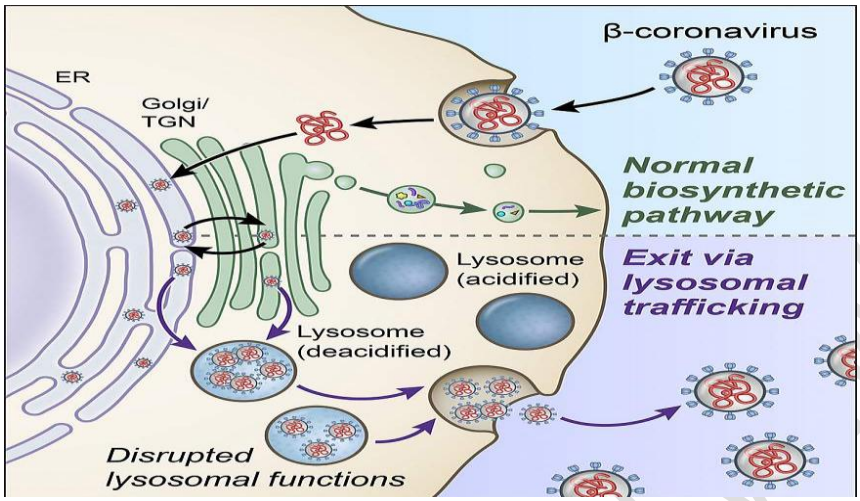

Figure 3. Exit of viruses through the Biosynthetic secretary pathways

Conventional wisdom has long held that most viruses including influenza, hepatitis C, and West Nile viruses exit through the so-called biosynthetic secretory pathway [9, 124]. That's a central pathway that cells use to transport hormones, growth factors, and other materials to their surrounding environment. Researchers have assumed that coronaviruses also use this pathway. In a pivotal experiment, researchers have found something different which exposed coronavirus-infected cells (specifically, mouse hepatitis virus) to certain chemical inhibitors known to block the biosynthetic pathway [15]. It was shocking to note that these coronaviruses got out of the cells just fine and this gave the first clue that maybe coronaviruses were using another pathway to exit cells. To look for that pathway, the researchers designed additional experiments using microscopic imaging and virus-specific markers involving human cells. They discovered that coronaviruses somehow target the lysosomes, which are highly acidic, and congregate there [44, 125].

That finding raised yet another question that if the coronaviruses are accumulating in lysosomes and lysosomes are acidic, why are the coronaviruses not destroyed before exiting? . In a series of advanced experiments, the researchers demonstrated that lysosomes get de-acidified in coronavirus-infected cells, significantly weakening the activity of their destructive enzymes. As a result, the viruses remain intact and ready to infect other cells when they exit [28, 60, 126]. This demonstrated that the coronavirus is well adapted to using these lysosomes to get out, but they're also disrupting the lysosome so it can't do its job or function. The researchers also discovered that disrupting normal lysosome function appears to harm the cells' immunological machinery. This very fundamental cell biology finding could help explain some of the things people are seeing in the clinic regarding immune system abnormalities in COVID patients like the cytokine storms, in which an excess of certain pro-inflammatory proteins in the blood of COVID patients overwhelm the immune system and cause high death rates [11, 96, 127].

Now that this mechanism has been identified, researchers may be able to find ways to disrupt this pathway and prevent lysosomes from delivering viruses to the outside of the cell; or re-acidify lysosomes in order to restore their normal functions in coronavirus-infected cells so they can fight COVID [88]. The authors have already identified one experimental enzyme inhibitor that potently blocks coronaviruses

from getting out of the cell. The lysosome pathway offers a whole different way of thinking about targeted therapeutics and further studies are needed to determine if such interventions will be effective and whether existing drugs can help block this pathway [41, 128].

CONCLUSION

Many critical questions still need answers about the effectiveness of COVID-19 vaccines within the framework of the current pandemic settings. There is a need o conduct post-introduction vaccine efficacy studies within selected countries to address these questions. COVID-19 vaccination has the potential to help protect people from getting COVID-19. Adults and pediatric population are predisposed to have some side effects from the vaccine, which are normal signs that the body has developed a defense or protection against the virus. These side effects have the potential to affect the ability of patients to perform their normal daily activities, although the effects may subside in a few days. Some subjects may not have any side effects, and allergic reactions may be rare. Serious adverse effects (SAE) that could cause a long-term health problem are extremely unlikely following any vaccination, including COVID-19 vaccination. Vaccine monitoring generally has shown that side effects may happen within six weeks of receiving a vaccine dose. The benefits of COVID-19 vaccination outweigh the known and potential risks.

With the increasing vaccine hesitancy especially in limited resources countries with limited access to vaccine, there is an increasing need for capacity building sensitization actors and strengthen sensitization, and education, for a better understanding of potential side effects. There is also the possibility to explore the efficiency of herd immunity protection from vaccinated population and those acquired from unvaccinated population. More studies on the toxicity of COVID-19 vaccines and other therapeutics drugs needs to be in constant exploitation, for continuous development and improvement on new therapeutic indications.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests ~~OR ,~~ non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Reference

1. Zheng C, Shao W, Chen X, Zhang B, Wang G, Zhang W Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. .Int J Infect Dis. 2022 Jan;114:252-260. doi: 10.1016/j.ijid.2021.11.009. Epub 2021 Nov 17.PMID: 34800687.

2. Nikolopoulou GB, Maltezou HC. COVID-19 in Children: Where do we Stand? .Arch Med Res. 2022 Jan;53(1):1-8. doi: 10.1016/j.arcmed.2021.07.002. Epub 2021 Jul 6.PMID: 34311990.
3. Chen Y, Xu Z, Wang P, Li XM, Shuai ZW, Ye DQ, Pan HF New-onset autoimmune phenomena post-COVID-19 vaccination. .Immunology. 2022 Apr;165(4):386-401. doi: 10.1111/imm.13443. Epub 2022 Jan 7.PMID: 34957554
4. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, Groome MJ, Huppert A, O'Brien KL, Smith PG, Wilder-Smith A, Zeger S, Deloria Knoll M, Patel MK. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease:

results of a systematic review and meta-regression. .Lancet. 2022 Mar 5;399(10328):924-944. doi: 10.1016/S0140-6736(22)00152-0. Epub 2022 Feb 23.PMID: 35202601.

5. Fu W, Sivajohan B, McClymont E, Albert A, Elwood C, Ogilvie G, Money D. Systematic review of the safety, immunogenicity, and effectiveness of COVID-19 vaccines in pregnant and lactating individuals and their infants. .Int J Gynaecol Obstet. 2022 Mar;156(3):406-417. doi: 10.1002/ijgo.14008. Epub 2021 Nov 13.PMID: 34735722.
6. Niebel D, Novak N, Wilhelmi J, Ziob J, Wilsmann-Theis D, Bieber T, Wenzel J and Braegelmann C. Cutaneous Adverse Reactions to COVID-19 Vaccines: Insights from an Immuno-Dermatological Perspective. Vaccines (Basel), 2021 ;9(9):944. doi: 10.3390/vaccines9090944.
7. Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, Miller J, Schrag SJ, Verani JR. Association Between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants.
8. .JAMA. 2022 Feb 15;327(7):639-651. doi: 10.1001/jama.2022.0470.PMID: 35060999

9. Gröber U, Holick MF. The coronavirus disease (COVID-19) - A supportive approach with selected micronutrients. .Int J Vitam Nutr Res. 2022 Jan;92(1):13-34. doi: 10.1024/0300-9831/a000693. Epub 2021 Jan 25.PMID: 33487035

10. Peeling RW, Heymann DL, Teo YY, Garcia PJ. Diagnostics for COVID-19: moving from pandemic response to control. .Lancet. 2022 Feb 19;399(10326):757-768. doi: 10.1016/S0140-6736(21)02346-1. Epub 2021 Dec 20.PMID: 34942102.

11. Lee ACK, Morling JR. COVID-19 vaccine dilemmas.Public Health. 2022 Jan;202:10-11. doi: 10.1016/j.puhe.2021.01.009. Epub 2021 Feb 1.PMID: 34875530.

12. Tembe-Fokunang EA, Awah KP, Banin AN, Dobgima JF, Nubia KC, Fokam J, Fokunang BL, Enoluomen EB, Igweze ZN,, Duerr R, Ondoua MTA, Tiskoff S, Fokunang, 2021. Medical anthropology, artificial intelligence and gain of function research perspective in the management of covid-19 pandemic in sub-Saharan Africa. EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH ; ejpmr, 2021,8(11), 76-90, SJIF Impact Factor 6.222; www.ejpmr.com

13. Dobgima JF Tembe EF, Ngwasiri PN , Noumo TN , Njinkio NB , Fokunang LB, Edrice AES, Bengyella Louis Tita BL, Kaba CN, Ejoh RA, Tita M and Fokunang CN. 2021. Nutritional Management Approach for Possible Prevention of Covid-19 Infection and Transmission in Sub-Saharan and Biodiversity Endowed Countries. Journal of Complementary and Alternative Medical Research 33(22): 39-58, 2021; Article no.JAMMR.70658 ISSN: 2456-8899 ; DOI: 10.9734/JAMMR/2021/v33i2231158; ISSN: 2231-0614, NLM ID: 101570965.

14. Wibawa T. COVID-19 vaccine research and development: ethical issues.
15. Trop Med Int Health. 2021 Jan;26(1):14-19. doi: 10.1111/tmi.13503. Epub 2020 Oct 19.PMID: 33012020 .

16. Ita K. Coronavirus Disease (COVID-19): Current Status and Prospects for Drug and Vaccine Development. .Arch Med Res. 2021 Jan;52(1):15-24. doi: 10.1016/j.arcmed.2020.09.010. Epub 2020 Sep 10.PMID: 32950264.

17. Franchini M, Liumbruno GM, Pezzo M. COVID-19 vaccine-associated immune thrombosis and thrombocytopenia (VITT): Diagnostic and therapeutic recommendations for a new syndrome. .Eur J Haematol. 2021 Aug;107(2):173-180. doi: 10.1111/ejh.13665. Epub 2021 Jun 9.PMID: 33987882

18. Lamb YN. BNT162b2 mRNA COVID-19 Vaccine: First Approval.
19. .Drugs. 2021 Mar;81(4):495-501. doi: 10.1007/s40265-021-01480-7.PMID: 33683637

20. Li YD, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC. Coronavirus vaccine development: from SARS and MERS to COVID-19. .J Biomed Sci. 2020 Dec 20;27(1):104. doi: 10.1186/s12929-020-00695-2.PMID: 33341119

21. Soleimanpour S, Yaghoubi A. COVID-19 vaccine: where are we now and where should we go? Expert Rev Vaccines. 2021 Jan;20(1):23-44. doi: 10.1080/14760584.2021.1875824. Epub 2021 Feb 17. PMID: 33435774

22. Salah HM, Mehta JL. COVID-19 Vaccine and Myocarditis. Am J Cardiol. 2021 Oct 15; 157:146-148. doi: 10.1016/j.amjcard.2021.07.009. Epub 2021 Jul 12. PMID: 34399967.

23. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2.Lancet Infect Dis. 2021 Feb;21(2): e26-e35. doi: 10.1016/S1473-3099(20)30773-8. Epub 2020 Oct 27. PMID: 33125914

24. Kamidani S, Rostad CA, Anderson EJ. COVID-19 vaccine development: a pediatric perspective. .Curr Opin Pediatr. 2021 Feb 1;33(1):144-151. doi: 10.1097/MOP.0000000000000978.PMID: 33278108

25. Klein SL, Creisher PS, Burd I.J. COVID-19 vaccine testing in pregnant females is necessary. Clin Invest. 2021; 131(5):e147553. doi: 10.1172/JCI147553.PMID: 33444286
26. *Greinacher A Thiele T; Theodore E.; Weisser KK, Paul A.; Eichinger S. "Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination". New England Journal of Medicine: NEJMoa2104840 (9 April 2021). doi:10.1056/NEJMoa2104840. PMID 33835769. Retrieved 16 September 2021.*
27. *Niebel D, Novak N, Wilhelmi J, Ziob J, Wilsmann-Theis D, Bieber T, Wenzel J and Braegelmann C. Cutaneous Adverse Reactions to COVID-19 Vaccines: Insights from an Immuno-Dermatological Perspective. Vaccines (Basel), 2021 ;9(9):944. doi: 10.3390/vaccines9090944.*
28. *Cines DB, Bussel T, James B. "SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia". New England Journal of Medicine (16 April, 2021): NEJMe2106315. doi:10.1056/NEJMe2106315. PMID 33861524. Retrieved 14 October 2021.*
29. *"AstraZeneca COVID-19 Vaccine (AZD1222)" (PDF). ACIP COVID-19 Emergency Meeting. AstraZeneca. 27 January 2021. Retrieved 05 Novemberl 2021.*
30. *"COVID-19 vaccine safety update: VAXZEVRIA"(PDF). European Medicines Agency. 28 March 2021. Retrieved 11 October, 2021.*
31. *"Janssen COVID-19 vaccine [Ad26.COV2. S, recombinant] Product monograph" (PDF). 5 March 2021. Retrieved 28 August, 2021.*

32. *Marks, Peter. "Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine". Retrieved 20 October, 2021.*
33. *Valeriani, Emanuele; Riva, Nicoletta; Nisio, Marcello Di; Ageno, Walter (22 October 2019). "Splanchnic Vein Thrombosis: Current Perspectives". Vascular Health and Risk Management. **15**: 449–461. doi:10.2147/VHRM.S197732. PMC 6815215.*
34. *Greinacher, Andreas; Thiele, Thomas; Warkentin, Theodore E.; Weisser, Karin; Kyrle, Paul A.; Eichinger, Sabine (9 April 2021). "Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination". New England Journal of Medicine: NEJMoa2104840. doi:10.1056/NEJMoa2104840.*
35. *Greinacher A, Selleng K, Warkentin TE. "Autoimmune heparin-induced thrombocytopenia". Journal of Thrombosis and Haemostasis. 2017; **15** (11): 2099–2114. doi:10.1111/jth.13813. PMID 28846826.*
36. *GACVS. Statement of the WHO Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee on safety signals related to the AstraZeneca COVID-19 vaccine". World Health Organization (19 March, 2021). Retrieved 23 October, 2021.*
37. Li YD, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC (December 2020). "Coronavirus vaccine development: from SARS and MERS to COVID-19". Journal of Biomedical Science. **27**(1): 104. doi:10.1186/s12929-020-00695-2. PMC 7749790. PMID 33341119.
38. Mullard A (30 November 2020). "How COVID vaccines are being divvied up around the world Canada leads the pack in terms of doses secured per capita". Nature. doi:10.1038/d41586-020-03370-6. PMID 33257891. S2CID 227246811.
39. So AD, Woo J (December 2020). "Reserving coronavirus disease 2019 vaccines for global access: cross sectional analysis". BMJ. **371**: m4750. doi:10.1136/bmj.m4750. ISSN 1756-1833. PMC 7735431. PMID 33323376.
40. Gao W, Tamin A, Soloff A, D'Aiuto L, Nwanegbo E, Robbins PD, et al. (December 2003). "Effects of a SARS-associated coronavirus vaccine in monkeys". Lancet. **362** (9399): 1895–96. doi:10.1016/S0140-6736(03)14962-8. PMC 7112457. PMID 14667748.
41. Greenough TC, Babcock GJ, Roberts A, Hernandez HJ, Thomas WD, Coccia JA, et al. (February 2005). "Development and characterization of a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody that provides effective immuno prophylaxis in mice". The Journal of Infectious Diseases. **191** (4): 507–14. doi:10.1086/427242. PMC 7110081. PMID 15655773.
42. Roberts A, Thomas WD, Guarner J, Lamirande EW, Babcock GJ, Greenough TC, et al. (March 2006). "Therapy with a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody reduces disease severity and viral burden in golden Syrian hamsters". The Journal of Infectious Diseases. **193** (5): 685–92. doi:10.1086/500143. PMC 7109703. PMID 16453264.
43. "SARS (severe acute respiratory syndrome)". National Health Service. 5 March 2020. Archived from the original on 9 March 2020. Retrieved 31 January 2020.
44. Shehata MM, Gomaa MR, Ali MA, Kayali G (January 2016). "Middle East respiratory syndrome coronavirus: a comprehensive review". Frontiers of Medicine. **10** (2): 120–36. doi:10.1007/s11684-016-0430-6. PMC 7089261. PMID 26791756.
45. Yong CY, Ong HK, Yeap SK, Ho KL, Tan WS (2019). "Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-Coronavirus". Frontiers in Microbiology. **10**: 1781. doi:10.3389/fmicb.2019.01781. PMC 6688523. PMID 31428074.
46. Le TT, Cramer JP, Chen R, Mayhew S (September 2020). "Evolution of the COVID-19 vaccine development landscape". Nature Reviews Drug Discovery. **19** (10): 667–68. doi:10.1038/d41573-020-00151-8. ISSN 1474-1776. PMID 32887942. S2CID 221503034.
47. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. (9 April 2020). "The COVID-19 vaccine development landscape". Nature Reviews Drug

Discovery. **19** (5): 305–06. doi:10.1038/d41573-020-00073-5. ISSN 1474-1776. PMID 32273591.
48. Simpson S, Kaufmann MC, Glozman V, Chakrabarti A (May 2020). "Disease X: accelerating the development of medical countermeasures for the next pandemic". The Lancet. Infectious Diseases. **20** (5): e108–15. doi:10.1016/S1473-3099(20)30123-7. ISSN 1474-4457. PMC 7158580. PMID 32197097.
49. Wee S (4 May 2020). "China's coronavirus vaccine drive empowers a troubled industry". The New York Times. ISSN 0362-4331. Archived from the original on 4 May 2020. Retrieved 4 May 2020.
50. Thorp HH (27 March 2020). "Underpromise, overdeliver". Science. **367** (6485): 1405. Bibcode:2020Sci...367.1405T. doi:10.1126/science. abb8492. PMID 32205459.
51. Blackwell T (20 April 2020). "COVID-19 vaccine researchers say pandemic lockdown placing many serious obstacles to their work". National Post. Archived from the original on 1 November 2020. Retrieved 3 May 2020.
52. "The drug development process". U.S. Food and Drug Administration (FDA). 4 January 2018. Archived from the original on 22 February 2020. Retrieved 12 April 2020.
53. Dubé E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J (1 August 2013). "Vaccine hesitancy: an overview". Human Vaccines and Immunotherapeutics. **9** (8): 1763–73. doi:10.4161/hv.24657. ISSN 2164-554X. PMC 3906279. PMID 23584253.
54. Abedi M (23 March 2020). "Canada to spend $192M on developing COVID-19 vaccine". Global News. Archived from the original on 9 April 2020. Retrieved 24 March 2020.
55. Takada N, Satake M (2 May 2020). "US and China unleash wallets in race for coronavirus vaccine". Nikkei Asian Review. Archived from the original on 10 May 2020. Retrieved 3 May 2020.
56. Cohen J (15 May 2020). "U.S. 'Warp Speed' vaccine effort comes out of the shadows". Science. **368** (6492): 692–93. Bibcode:2020Sci... 368..692C. doi:10.1126/science.368.6492.692. ISSN 0036-8075. PMID 32409451.
57. "World Health Organization timeline – COVID-19". World Health Organization. 27 April 2020. Archived from the original on 29 April 2020. Retrieved 2 May 2020.
58. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. (9 April 2020). "The COVID-19 vaccine development landscape". Nature Reviews Drug Discovery. **19** (5): 305–06. doi:10.1038/d41573-020-00073-5. ISSN 1474-1776. PMID 32273591.
59. Gates B (February 2020). "Responding to Covid-19: A once-in-a-century pandemic?". The New England Journal of Medicine. **382** (18): 1677–79. doi:10.1056/nejmp2003762. PMID 32109012.
60. Fauci AS, Lane HC, Redfield RR (March 2020). "Covid-19: Navigating the uncharted". The New England Journal of Medicine. **382** (13): 1268–69. doi:10.1056/nejme2002387. PMC 7121221. PMID 32109011.
61. TT, Cramer JP, Chen R, Mayhew S (4 September 2020). "Evolution of the COVID-19 vaccine development landscape". Nature Reviews Drug Discovery. **19** (10): 667–68. doi:10.1038/d41573-020-00151-8. ISSN 1474-1776. PMID 32887942. S2CID 221503034.
62. Ahmed DD (4 June 2020). "Oxford, AstraZeneca COVID-19 deal reinforces 'vaccine sovereignty'". Stat. Archived from the original on 12 June 2020. Retrieved 8 June 2020.
63. "WHO 'backed China's emergency use' of experimental Covid-19 vaccines". South China Morning Post. 25 September 2020. Archived from the original on 26 September 2020. Retrieved 26 September 2020.
64. Kramer AE (19 September 2020). "Russia Is Slow to Administer Virus Vaccine Despite Kremlin's Approval". The New York Times. ISSN 0362-4331. Archived from the original on 27 September 2020. Retrieved 28 September 2020.

65. "Pfizer and BioNTech to Submit Emergency Use Authorization Request Today to the U.S. FDA for COVID-19 Vaccine". Pfizer (Press release). 20 November 2020. Retrieved 20 November 2020.
66. Park A (20 November 2020). "Exclusive: Pfizer CEO Discusses Submitting the First COVID-19 Vaccine Clearance Request to the FDA". Time. Retrieved 20 November 2020.
67. Thomas K, LaFraniere S, Weiland N, Goodnough A, Haberman M (12 December 2020). "F.D.A. Clears Pfizer Vaccine, and Millions of Doses Will Be Shipped Right Away". The New York Times. Retrieved 12 December 2020.
68. "Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern". World Health Organization. 26 November 2021. Archived from the original on 26 November 2021. Retrieved 26 November 2021.
69. Parekh, Marcus; Platt, Poppie; Team, Global Health Security; Barnes, Joe (26 November 2021). "Coronavirus latest news: EU suspends all flights to southern Africa over omicron Covid variant fears". The Telegraph. ISSN 0307-1235. Archived from the original on 26 November 2021. Retrieved 26 November 2021.
70. Meyer, David (26 November 2021). "What's Omicron? Here's what we know and don't know about the new COVID variant that's roiling markets and air travel". Fortune. Archived from the original on 26 November 2021. Retrieved 26 November 2021.
71. Torjesen, Ingrid (29 November 2021). "Covid-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear". BMJ. **375**: n2943. doi:10.1136/bmj.n2943. ISSN 1756-1833. PMID 34845008.
72. Patel, Vimal (27 November 2021). "How Omicron, the New Covid-19 Variant, Got Its Name". The New York Times. ISSN 0362-4331. Archived from the original on 28 November 2021. Retrieved 28 November 2021.
73. Falcon, Russell (29 November 2021). "It's 'omicron,' not 'omnicron': COVID variant's spelling doesn't have two Ns". KXAN. Retrieved 1 December 2021.
74. Brandt, Joe (30 November 2021). "Omicron or Omnicron? How To Pronounce the Latest COVID-19 Variant". NBC Lx. Retrieved 1 December 2021.
75. Heaney, Katie (1 December 2021). "What We Know About the Omicron Variant So Far". The Cut. Retrieved 1 December 2021.
76. "What Do You Need To Know About Omicron? Biden Says Be Concerned But Don't Panic". NPR. 29 November 2021. Retrieved 1 December 2021
77. "FDA Takes Additional Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for Second COVID-19 Vaccine". U.S. Food and Drug Administration (FDA)(Press release). Retrieved 18 December 2020.
78. Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, et al. (December 2020). "The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine — United States, December 2020" (PDF). MMWR. Morbidity and Mortality Weekly Report. **69** (5152): 1653–1656. doi:10.15585/mmwr.mm695152e1. PMID 33382675. S2CID 229945697.
79. Park KS, Sun X, Aikins ME, Moon JJ (December 2020). "Non-viral COVID-19 vaccine delivery systems". Advanced Drug Delivery Reviews. **169**: 137–51. doi:10.1016/j.addr.2020.12.008. PMC 7744276. PMID 33340620.
80. Kowalski PS, Rudra A, Miao L, Anderson DG (April 2019). "Delivering the Messenger: Advances in Technologies for Therapeutic mRNA Delivery". Mol Ther. **27** (4): 710–28. doi:10.1016/j.ymthe.2019.02.012. PMC 6453548. PMID 30846391.
81. Verbeke R, Lentacker I, De Smedt SC, Dewitte H (October 2019). "Three decades of messenger RNA vaccine development". Nano Today. **28**: 100766. doi:10.1016/j.nantod.2019.100766.
82. Palca J (27 July 2020). "COVID-19 vaccine candidate heads to widespread testing in U.S." NPR. Archived from the original on 11 October 2020. Retrieved 27 July 2020.

83. O'Reilly P (26 May 2020). "A Phase III study to investigate a vaccine against COVID-19". ISRCTN. doi:10.1186/ISRCTN89951424. ISRCTN89951424.
84. Johnson, Carolyn; McGinley, Laura. "Johnson & Johnson seeks emergency FDA authorization for single-shot coronavirus vaccine". The Washington Post.
85. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, et al. (February 2018). "Adaptive designs in clinical trials: why use them, and how to run and report them". BMC Medicine. **16** (1): 29. doi:10.1186/s12916-018-1017-7. PMC 5830330. PMID 29490655.
86. Farge, Emma; Revill, John (5 January 2021). "WHO recommends two doses of Pfizer COVID-19 vaccine within 21–28 days". Reuters. Geneva. Retrieved 5 March 2021.
87. Keaten, Jamey (8 January 2021). "WHO: Amid short supplies, vaccine doses can be 6 weeks apart". Associated Press. Geneva. Retrieved 6 March 2021.
88. Jones, Ian; Roy, Polly (2 February 2021). "Sputnik V COVID-19 vaccine candidate appears safe and effective". The Lancet. **397** (10275): 642–643. doi:10.1016/S0140-6736(21)00191-4. PMC 7906719. PMID 33545098.
89. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. (February 2021). "Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia". The Lancet. **397** (10275): 671–681. doi:10.1016/S0140-6736(21)00234-8. ISSN 0140-6736. PMC 7852454. PMID 33545094.
90. Walsh N, Shelley J, Duwe E, Bonnett W (27 July 2020). "The world's hopes for a coronavirus vaccine may run in these health care workers' veins". São Paulo: CNN. Archived from the original on 3 August 2020. Retrieved 3 August 2020.
91. Gallagher, James; Triggle, Nick (30 December 2020). "Covid-19: Oxford-AstraZeneca vaccine approved for use in UK". BBC. Retrieved 5 March 2020.
92. AstraZeneca COVID-19 Vaccine (PDF) (Product Monograph). AstraZeneca. 26 February 2021. 244627. Retrieved 5 March 2021.
93. Voysey M, Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. (19 February 2021). "Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials". The Lancet. **397** (10277): 881–891. doi:10.1016/S0140-6736(21)00432-3. Retrieved 10 March 2021.
94. Xia, Shengli; Zhang, Yuntao; Wang, Yanxia; Wang, Hui; Yang, Yunkai; Gao, George; et al. (15 October 2020). "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial". The Lancet Infectious Diseases. **21** (1): 39–51. doi:10.1016/S1473-3099(20)30831-8. PMC 7561304. PMID 33069281.
95. Elbahrawy, Farah; Lyu, Dong; Omar, Abeer; Che, Claire; Paton, James (9 December 2020). "China State-Backed Covid Vaccine Has 86% Efficacy, UAE Says". Bloomberg News. Retrieved 5 March 2020. CNBG's vaccine can be transported and stored at normal refrigerated temperatures.
96. Wee S, Qin A (30 December 2020). "A Chinese Covid-19 Vaccine Has Proved Effective, Its Maker Says". The New York Times. Retrieved 30 December 2020.
97. Yang Y. "A Study to Evaluate The Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines (Vero Cell) in Healthy Population Aged 18 Years Old and Above". ClinicalTrials.gov. Archived from the original on 14 September 2020. Retrieved 15 September 2020.
98. "Bahrain allows Sinopharm COVID-19 vaccine candidate use in frontline workers". MSN. Reuters. Retrieved 3 November 2020.
99. Tan, Yvette (14 January 2021). "Covid: What do we know about China's coronavirus vaccines?". BBC. Retrieved 5 March 2020.

100. Soeriaatmadja W (11 January 2021). "Indonesia grants emergency use approval to Sinovac's vaccine, local trials show 65% efficacy". The Straits Times. Retrieved 11 January 2021.
101. "Sinovac: Brazil results show Chinese vaccine 50.4% effective". BBC News. 13 January 2021. Retrieved 12 February 2021.
102. Baden L, Essink B, Kotloff K, Frey S, Novak R, Diemert D, et al. (December 2020). "Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine". New England Journal of Medicine. **384** (5): 403–416. doi:10.1056/NEJMoa2035389. PMC 7787219. PMID 33378609.
103. Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19 (Briefing). Food and Drug Administration. 26 February 2021. p. 6. Retrieved 6 March 2021. The vaccine, known as Ad26.COV2.S, is a replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S protein.
104. Ledford H (29 January 2021). "J&J's one-shot COVID vaccine offers hope for faster protection". Nature. doi:10.1038/d41586-021-00119-7. PMID 33526898.
105. "Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 ENSEMBLE Trial" (Press release). Johnson & Johnson. 29 January 2021. Retrieved 29 January 2021.
106. "Janssen COVID-19 Vaccine - ad26.cov2.s injection, suspension". DailyMed. U.S. National Institutes of Health. Retrieved 15 March 2021.
107. Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH, et al. (August 2020). "Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial". Lancet. **396** (10249): 479–88. doi:10.1016/s0140-6736(20)31605-6. ISSN 0140-6736. PMC 7836858. PMID 32702299. Lay summary.
108. Peshimam, Gibran; Farooq, Umar (8 February 2021). "CanSinoBIO's COVID-19 vaccine 65.7% effective in global trials, Pakistan official says". Reuters. Islamabad. Retrieved 5 March 2021. its single-dose regimen and normal refrigerator storage requirement could make it a favourable option for many countries
109. Lazcano P (15 November 2020). "Así funcionan las cuatro vacunas que se probarán en Chile". La Tercera. Retrieved 15 December 2020.
110. Martinez AI (3 November 2020). "CanSino Biologics delivers COVID-19 vaccine to Mexico for late-stage trial". Reuters. Retrieved 4 November 2020.
111. Ng E (28 October 2020). "China's CanSino trials Covid-19 vaccine in 'high disease burden' nations". South China Morning Post. Retrieved 4 November 2020.
112. Nafisa E (9 August 2020). "CanSino to start Phase III trial of COVID-19 vaccine in Saudi". Reuters. Retrieved 4 November 2020.
113. Gou J. "Phase III Trial of A COVID-19 Vaccine of Adenovirus Vector in Adults 18 Years Old and Above". ClinicalTrials.gov. Archived from the original on 18 September 2020. Retrieved 17 September 2020.
114. Ryumin, Alexander (20 February 2021). "Russia registers its third COVID-19 vaccine CoviVac". TASS. Moscow. Retrieved 6 March 2021.
115. Ivanova, Polina (8 February 2021). "Russia approves its third COVID-19 vaccine, CoviVac". Reuters. Moscow. Retrieved 5 March 2021. The CoviVac shot is given in two doses, 14 days apart. It is transported and stored at normal fridge temperatures, of 2 to 8 degrees Celsius (35.6 to 46.4 Fahrenheit), Deputy Prime Minister Tatiana Golikova said in a government briefing in January.
116. Rojas M, Rodríguez Y, Monsalve DM, etal. Convalescent plasma in Covid-19: Possible mechanisms of action. AutoimmunRev2020; 19:102554. doi: 10.1016/j.autrev.2020.102554 pmid: 32380316.
117. Subbarao K, Mordant F, Rudraraju R. Convalescent plasma treatment for COVID-19: Tempering expectations with the influenza experience. EurJImmunol2020; 50:1447-53. doi: 10.1002/eji.202048723 pmid: 32886952.

118. Piechotta V, Chai KL, Valk SJ, etal. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. CochraneDatabaseSystRev 2020;7: CD013600.pmid: 32648959.
119. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra Pthe PLACID Trial Collaborators. Convalescent plasma in the management of moderate COVID-19 in India: An open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial). BMJ 2020;m3939.
120. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA, 2020;324:782-93. doi: 10.1001/jama.2020.12839 pmid: 32648899.
121. Estcourt LJ, Roberts DJ. Convalescent plasma for covid-19. BMJ2020;370:m3516. doi: 10.1136/bmj.m3516 pmid: 32933945.
122. Lapid N. Common cold antibiotics hold due to COVID-19 behaviors, lung scans speed COVID-19 diagnosis in stroke patients. Healthcare Pharmac, Nov 2020 at 7.46PM.
123. NIH. Scientist discover key pathways in lysosomes that coronavirus use to exit cells. Biology and Microbiology, Oct 29 2020.
124. Sourish G, Teegan A, Dellibovi R, Kervil A et al. B coronavirus uses lysosomes from egress instead of the biosynthetic secretary pathway. Biology & Microbiology, oct 27, 2020. DOI: https??doi.org??10.1016/j.cell. 2020.10.039.
125. NIH. Targeting cells trash compactor could lead to new antiviral strategy to fight COVID-19. National Heart, Lung and Blood Institute Oct, 28, 2020.