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Review Article

Retrospective View of COVID-19 Pandemic: Treatment, Management and Development of Preventive Measures

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Abstract

SARS-CoV-2 has held the world hostage over the last 3 years, constantly mutating to elude therapeutic measures, with 765,903,278 documented cases and 6,927,378 deaths as of May 17th, 2023. During this time, biotechnology hastened advancement of preventive measures, with healthcare professionals repurposing the use of existing medications to manage the onslaught of infections and deaths. In this retrospective review, we revisit the emergency use authorization of nascent vaccines, repurposing of non-antiviral medications and stand-by convalescent plasma and immunotherapies while welcoming the development of innovative gene editing tools.

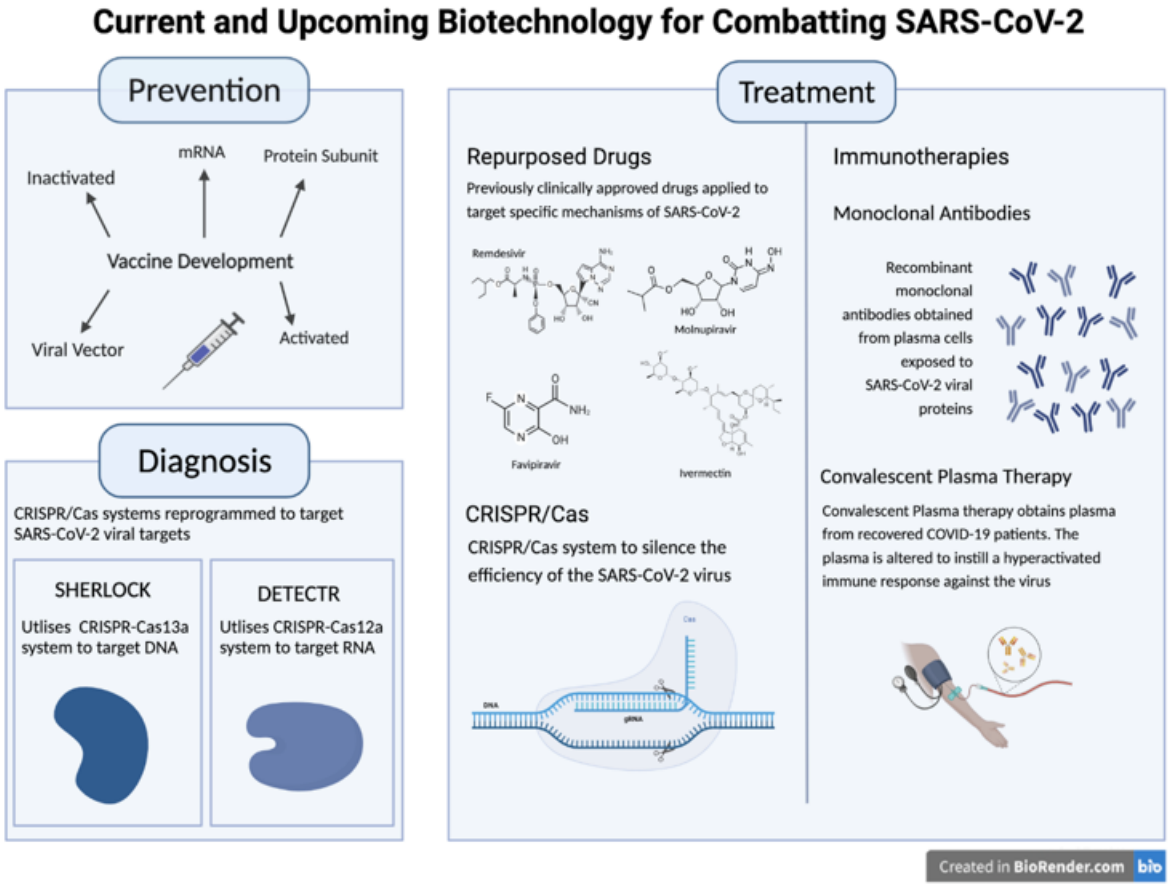

Figure 1: Graphical Abstract summarizing current and emerging biotechnology utilized medically for the prevention, diagnosis, and treatment of COVID-19. *Graphic made with BioRender.com.*

Keywords: COVID-19; CRISPR; Immunotherapy; Management; Prevention; Repurposing; SARS-CoV-2; Treatment; Vaccine.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the pathogenic virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first identified in December 2019 [1], ultimately resulting in the largest global health crisis in a century. On March 12, 2020, World Health Organization (WHO) declared COVID-19 a global pandemic [2]. Since then, SARS-CoV-2 has wreaked havoc on global health and economics. At the time of writing (May 17th, 2023), the virus is responsible for over 765 million infections and 6.9 million deaths worldwide [3]. A timeline of SARS-CoV-2 development is shown in Figure 2.

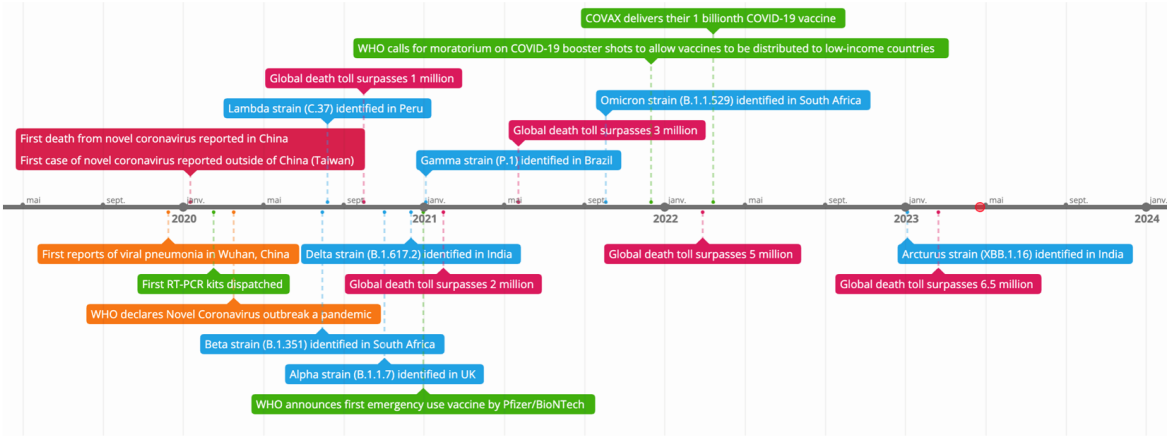

Figure 2: Timeline of major COVID-19 events and the development of SARS-CoV-2. *Graphic made with BioRender.com.*

SARS-CoV-2 shares approximately 80% homology with SARS-CoV-1, with the disparity responsible for mutations in the COVID-19 spike protein [4]. SARS-CoV-2 enters through the respiratory tract before attaching to cell surface receptor proteins, like Angiotensin-Converting Enzyme 2 (ACE2), through its homotrimer spike. Following receptor-mediated cell-entry it is directly translated by host ribosomes, particularly in the epithelial linings of the lungs, kidneys, and heart [5].

SARS-CoV-2 mutates rapidly. In February 2020 spike protein mutation A23403G (D614G) emerged, increasing viral fitness and infectivity [6]. The single nucleotide substitution in the spike protein receptor binding domain increased affinity to the ACE2 receptor and heightened its replication in human cells [7]. Rolling genomic mutations continue to affect both broader viral fitness, such as transmissibility and infectivity, and pandemic containment measures such as detection and vaccination [8]. Notable strains include Alpha (B.1.1.7), Beta (B.1.351.), Gamma (P.1) and Delta (B.1.617.2), the latter of which developed a significantly higher viral load (up to 1,200 times greater than the ancestral virus) and a shorter incubation period [9].

The dominant strain Omicron (B.1.1.529), first reported in South Africa in late 2021 [10], was classified as a 'variant of concern' (VOC) by WHO from initial detection [11]. Though health outcomes are less severe, it is highly contagious and carries genetic variations causing increased transmissibility and vaccine evasion [12]. One of these genetic variations also leads to 'S gene dropout' or 'target failure', where one of the genetic sections targeted by polymerase chain reaction (PCR) testing gives a false negative [13]. Omicron (BA.5) and its subvariants have dominated the sequenced cases lodged with GISAID since May 2022 through the end of the year (85%) [14]. WHO's most recent variant of interest is Arcturus (XBB.1.16), due to its growth advantage and immune evasion [15]. First discovered in January 2023 in India, it has spread to 31 countries [15].

As of May 17th, 2023, there are 199 vaccines in pre-clinical development. Eleven vaccines have WHO emergency authorization [16] via four main platforms: mRNA, viral vector, inactivated and protein subunit.

Repurposing pre-existing drugs for the treatment of SARS-CoV-2 is efficient and cost-effective [17].{Singh, 2020 #63} Computational and biological experimental methods can identify approved pharmaceuticals that target specific SARS-CoV-2 mechanisms using molecular docking, signature matching and genome-wide associated studies [18]. Alternatively, experimental methods including assays and phenotypic screening can identify effective drugs [19]. Pre-existing candidates have already undergone risk assessments in both preclinical models and humans, making this significantly more efficient and economical than standard drug development [17, 19]. For example, nirmatrelvir was originally developed for the treatment of hepatitis C, it is now packaged alongside ritonavir as Paxlovid by Pfizer. Phase 3 trials showed that among people with COVID-19 who were at high risk of hospitalization or death, those who received Paxlovid had a 90% lower risk of the above than placebo [20].

Immunotherapeutic approaches have shown clinical benefits in patients with Influenza, SARS, and Middle East Respiratory Syndrome (MERS) [21], suggesting potential for SARS-CoV-2 treatment. However, the complexity of COVID-19's immune avoidance mechanisms and associated pro-inflammatory events, such as cytokine storm and T cell exhaustion, have prevented isolating a single effective approach. In response to the pandemic's urgency, the Food and Drug Administration (FDA) authorized emergency use of immunotherapy methods such as recombinant monoclonal antibodies (rMAB) and convalescent plasma (CP) therapy. Alternatively, CP therapy utilizes plasma from recovered COVID-19 patients to impede infection and mitigate hyperactivated immune reaction. Some promising immunotherapeutic approaches are undergoing trials. The most notable are the inhaled interferon

β-1α (IFNβ-1α) and peg-interferon λ-1 (peg-IFNλ-1) based immunotherapies, interleukin-6 (IL-6) blockade and Janus kinase (*JAK*) inhibition [22].

Gene-editing is the most novel technology applied to SARS-CoV-2. It has been tailored to virus degradation, detection, and diagnosis [23-25]. The CRISPR/Cas systems have enormous potential due to their precision, efficiency and cost-effectiveness [24]. Figure 3 explains the guide RNA and Cas enzyme process. CRISPR-based diagnostic technologies include endonuclease-targeted CRISPR trans reporter (DETECTR) and Specific High-sensitivity Enzymatic Reporter un-LOCKing (SHERLOCK). As a treatment, CRISPR-Cas13-based strategies such as Prophylactic Antiviral CRISPR in huMAN cells (PAC-MAN) have strong potential for virus degradation in humans [26].

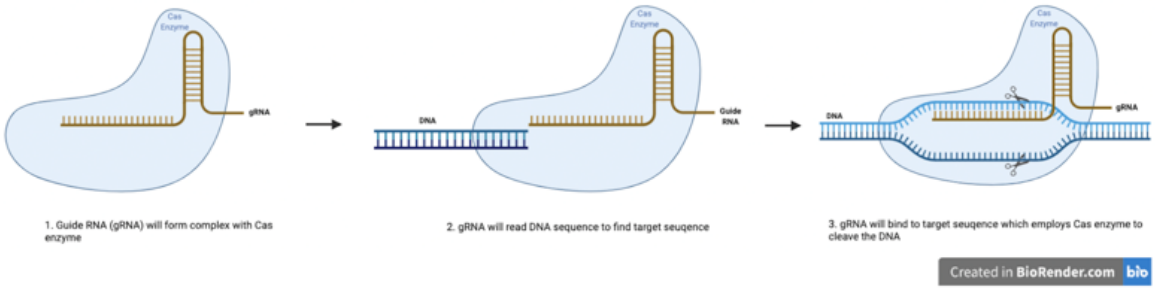

Figure 3: Graphical flow of CRISPR-Cas mechanism. *Graphic made with BioRender.com.*

Review Methodology

This investigation began with keyword searches in databases including PubMed, Research Gate, New England Journal of Medicine, World Health Organization (WHO), International Medical University library database, University of New South Wales library database, University of Wollongong library database and the Clinicaltrials.gov platform. Research took place from December 15th, 2021, to May 17th , 2023. The key topics were vaccines, repurposed drugs, immunotherapy and CRISPR. For each topic keywords were targeted across databases. Primary source articles were selected and clinical trial records were searched through Clinicaltrials.gov, using "COVID-19" as the condition/disease keyword. Completed clinical trials, novel treatments and vaccines with promising results were analyzed. Figure 4 summarizes the methods used to evaluate the sources used in this review. Figures were produced through BioRender, Lucidchart and Time Graphics.

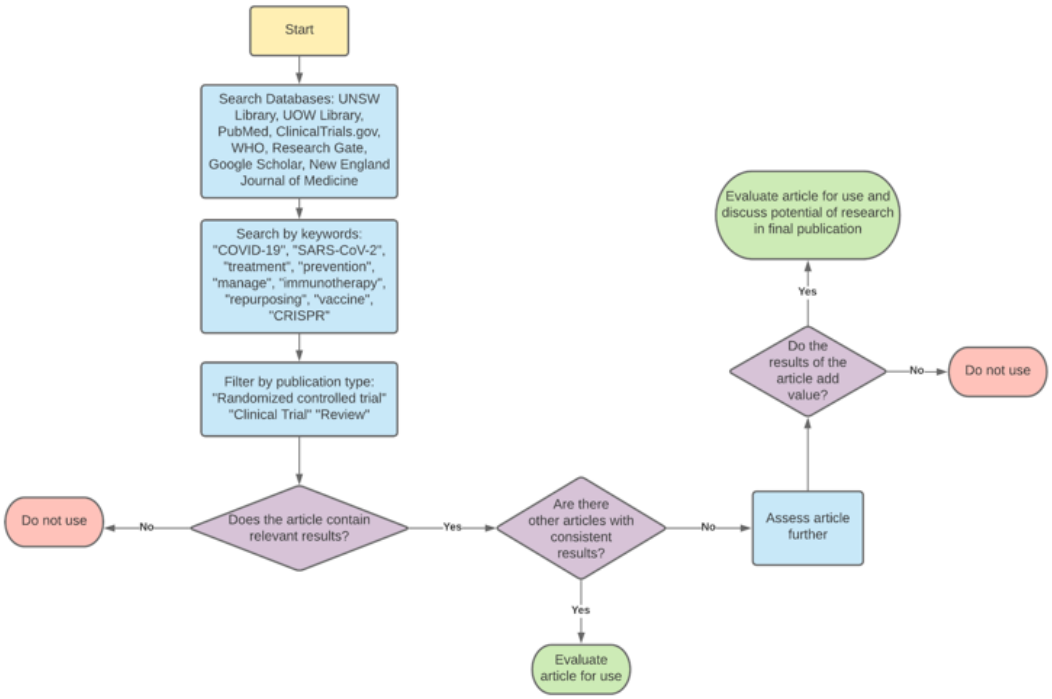

Figure 4: Methodological approach to determine suitability of source material. *Created with Lucidchart.com*

Preventive Measures

Vaccines

Vaccines are our most successful tool to prevent severe illness and death from COVID-19 [27]. Their development has been accelerated by partnerships between institutions and governments. Many vaccines were approved quickly under WHO's emergency use criteria, which requires at least 50% efficacy, 6-month protection, usability in older adults and a maximum of 2 doses [28]. Among those to receive emergency use approval from WHO within one year of the outbreak are Pfizer/BioNTech, Covishield, Janssen, Moderna and AstraZeneca.

There are currently 50 vaccines approved by at least 1 country, and 11 approved by WHO [16]. Pfizer/BioNTech's mRNA vaccine, Moderna's mRNA vaccine, Oxford/AstraZeneca's non-replicating viral vector vaccine, Johnson & Johnson's non-replicating viral vector vaccine and Sinopharm's inactivated vaccine are the most widely used and approved globally [16]. Most vaccines in clinical trials are protein subunit (32%) or non-replicating viral vector (14%) [29], with no WHO-approved replicating viral vector or live attenuated. *(Table S1, Figure S1 and Figure S2 in Supplementary Materials)*

Vaccine	Modality	Developer	Number of Countries (Approval and Trials)	Date of Emergency Use Listing by WHO	Reference
mRNA-1273 (Spikevax)	RNA	Moderna	86 approved countries, 63 trials (22 countries)	30 April 2021	S1
BNT162b2 (Comirnaty)	RNA	Pfizer / BioNTech	146 approved countries, 80 trials in 26 countries	31 December 2020	S2
Ad26.COV2.S	Non-Replicating Viral Vector	Janssen (Johnson & Johnson)	111 approved countries, 23 trials (23 countries)	12 March 2021	S3
AZD1222 (ChAdOx1/ Vaxzevria)	Non-Replicating Viral Vector	Oxford / AstraZeneca	140 approved countries, 63 trials (30 countries)	16 April 2021	S4
Covishield	Non-Replicating Viral Vector	Serum Institute of India (Oxford/AstraZeneca formulation)	49 approved countries, 4 trials (1 country)	15 February 2021	S5
Convidecia	Non-Replicating Viral Vector	CanSino	10 countries, 13 trials (6 countries)	19 May 2022	S6
Covaxin	Inactivated	Bharat Biotech	14 approved countries, 14 trials (2 countries)	3 November 2021	S7
Covilo	Inactivated	Sinopharm (Beijing)	91 approved countries, 29 trials (12 countries)	7 May 2021	S8
CoronaVac	Inactivated	Sinovac	56 approved countries, 37 trials (9 countries)	1 June 2021	S9
Nuvaxoid	Protein Subunit	Novavax	37 approved countries, 16 trials in 12 countries	21 December 2021	S10
COVOVAX (Novavax formulation)	Protein Subunit	Serum Institute of India (uses Novavax formulation)	5 approved countries, 3 trials (1 country)	20 December 2021	S11

Table S1: Vaccines approved for use by WHO and their date of emergency use listing, including RNA vaccines, viral vector vaccines (non-replicating), inactivated vaccines, and protein subunit vaccines.

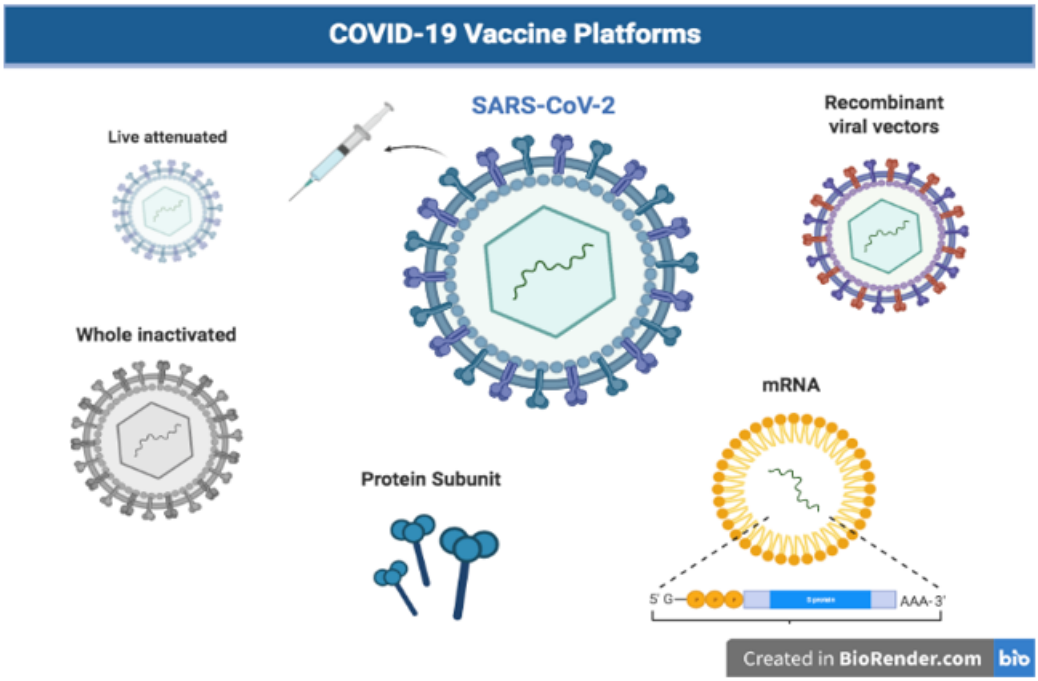

Figure S1: Graphic representation of the vaccine platforms explored. They include mRNA, recombinant viral vector (replicating and non-replicating), whole inactivated, live attenuated, and protein subunit vaccines. Adapted from "Approaches to Viral Vaccine Development", by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates

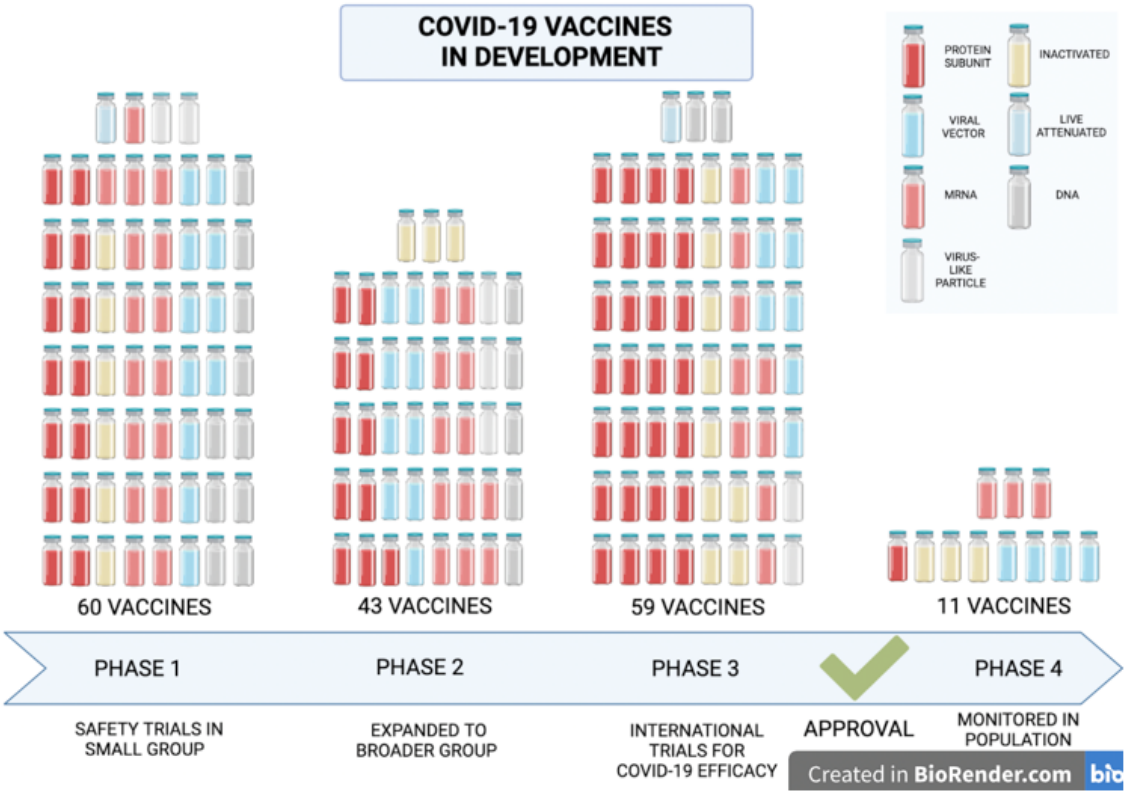

Figure S2: Progression of vaccines through stages of clinical trials, organized by platform. Data taken from WHO[29] Graphic made with BioRender.com. Phase 1 trials test new vaccines in a small group first, to assess safety profiles. Phase 2 trials expand testing to a larger group after a vaccine is found to be safe in Phase 1 trials, to identify any adverse side effects. Phase 3 trials are run on different populations across various regions or countries and are typically run right before a vaccine meets approval. After approval the vaccine is monitored long-term in phase 4 trials, across a broader population to ensure its safety and efficacy.

mRNA vaccines became the first COVID-19 vaccine to receive emergency use approval from WHO. Less than a year into the pandemic, Pfizer/BioNTech was approved on December 31, 2020 [30]. Progress on coronavirus vaccines from previous outbreaks, SARS-CoV-1 and MERS-CoV, greatly accelerated development. MERS-CoV has 9 vaccines reach phase I/II trials, including the ChAdOx non-replicating adenovirus vector vaccine expressing the full-length S protein [31]. This vaccine was adapted for SARS-CoV-2 by Oxford and AstraZeneca.

In the early months in 2022, both Pfizer and Moderna adapted to the '*strain of the moment*' and developed Omicron-tailored vaccines. Pfizer's Omicron formula has shown substantially higher neutralizing antibody responses against Omicron BA.1.35 [32, 33], while Moderna's Omicron-specific booster vaccine (mRNA-1273.529) elicits superior neutralizing antibody responses against BA.4 and BA.5 than the original formulation (mRNA-1273) [34, 35].

There are many promising vaccines in development; however, the difficulty in developing a safe and effective vaccine is evidenced in the slow progress and abandonment of candidates. For example, CureVac's mRNA vaccine phase I trials showed more than 70% efficacy against moderate-to-severe infection. Efficacy dropped to just 48% in phase III trials [36], hence, it was abandoned in October 2021. Outlines for selected promising candidate vaccines are summarized in Table 1 at the end of the vaccines section. Ultimately, the success of vaccination efforts in pandemic control will continue to depend on widespread distribution and uptake of effective vaccines, as well as adaptation of strategies in response to emerging variants.

Name	Modality	Developer	Efficacy	Clinical Trial Progress	References
CVnCOV	mRNA	CureVac AG	70.7% vaccine efficacy against moderate to severe COVID-19 in phase I trials. 48% efficacy in phase III trials.	Abandoned in 2021 due to low efficacy in phase III.	36
ARCoV (Walvax)	mRNA	Academy of Military Sciences (AMS), Walvax biotechnology and Suzhou Abogen biosciences	N/A: in trial	Phase III	84
ARCT-154	mRNA	Arcturus Therapeutics, Inc.	N/A: in trial	Phase III	85
mRNA-1273.351 (Beta-variant adapted)	mRNA	Moderna	N/A: in trial	Phase IV	43, 86, 87
mRNA-1273.529 (Omicron-variant adapted)	mRNA	Moderna	N/A: in trial	Phase II/III	34, 88
Ad5-nCoV (Convidecia)	Non-replicating viral vector	CanSino Biological Inc. / Beijing Institute of Technology	N/A: in trial	Phase III	89, 90
Ad5-nCoV-IH (Convidecia) for inhalation	Non-replicating viral vector (Inhaled)	CanSino Biological Inc. / Beijing Institute of Technology	N/A: in trial	Phase IV	91
Sputnik V + Sputnik Light	Non-replicating viral vector Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S)	Gamaleya Research Institute, Health Ministry of the Russian Federation	N/A: in trial	Sputnik V: Phase III Sputnik Light: Phase III	92-95
DelNS1-2019-nCoV-RBD-OPT1	Replicating viral vector (Intranasal flu-based-RBD)	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy	N/A: in trial	Phase III	29, 81
rVSV-SARS-CoV-2-S Vaccine (IIBR-100)	Replicating Viral Vector	Israel Institute for Biological Research	N/A: in trial	Phase II/III	80
Turkovac	Inactivated	Health Institutes of Turkey	N/A: In trial	Phase III	96
QazVac	Inactivated	Kazakhstan RIBSP	N/A: In trial	Phase III	97
(Inactivated) VERO cells	Inactivated	Sinopharm (Wuhan)	N/A: in trial	Phase III	98, 99
COVI-VAC	Live Attenuated Vaccine	Codagenix Inc	COVI-VAC is considered well tolerated in healthy young adults; however, vaccine has limited trials currently	Phase III	82

MV-014-212	Live Attenuated Vaccine	Meissa Vaccines	"Stimulated a strong nasal IgA antibody response in seropositive and seronegative adults"	Phase I	83
V-01-351/V-01D Bivalence Vaccine (Omicron)	Protein Subunit	Livzon Pharmaceutical Group	N/A: in trial	Phase III	29
SpikoGen	Protein Subunit	Vaxine and CinnaGen	Vaccine is safe, produces immune response, and was well tolerated in all participants	Phase III	100, 101
Medigen: MVC-COV1901	Protein Subunit	Medigen Vaccine Biologics Corp	Vaccine shows good safety profile with promising immune responses	Phase IV	102
NVX-CoV2373	Protein Subunit	Novavax	"A two-dose regimen of the NVX-CoV2373 vaccine administered to adult participants conferred 89.7% protection against SARS-CoV-2 infection "	Phase III	73, 103, 104
N/A: Not applicable					

Table 1: Summary of promising candidate vaccines for SARS-CoV-2, including trial progression.

mRNA Vaccines

mRNA vaccines are extremely effective in preventing severe COVID-19 as transfected mRNAs express antigen proteins *in vivo,* inducing robust humoral and cellular immune responses [37]. mRNA vaccines are manufactured by synthesizing the mRNA sequence that encodes the viral protein of interest, normally the spike protein for SARS-CoV-2. The manufactured mRNA is protected during delivery to the host by advancements such as lipid nanoparticle (LNP) biotechnology [38]. The encapsulated mRNA is then formulated with other necessary components to create the final vaccine product and administered intramuscularly. There are two WHO-approved mRNA vaccines: Pfizer (Oxford/AstraZeneca) and SpikeVax (Moderna) [16].

mRNA vaccines are WHO-authorized for use in children, with Pfizer BNT162b2 approved for children 5 years and older and Moderna approved for 12 years and older [39]. Trials have shown both vaccines to be safe for their respective age groups, with an overall efficacy of 90.7% for Pfizer in 5 to 11-year-olds [40] and 92.7% for Moderna in adolescents [41].

Moderna, Pfizer and Livzon have targeted specific variants with their mRNA platforms. mRNA vaccines offer high adaptability in responding to emerging strains of SARS-CoV-2 by allowing delivery of a transcript that encodes a specific immunogen or antigen. This versatility has already proven itself in the wake of Omicron. In December 2021 a South African study found that protection against hospitalization from SARS-CoV-2 by Pfizer/BioNTech's vaccine dropped from 93% to 70% across two monitoring periods [42]. The key difference was the emergence of the Omicron variant, highlighting the need for tailored vaccines.

Moderna's first multivalent vaccine contained both the mRNA-1273 (original) and mRNA-1273.351 (Beta) strains [43]. Booster shots using this hybrid indicated strong B cell memory response and increased neutralizing antibody titres compared to the original vaccine alone [43]. Moderna also combined their ancestral formula with the Omicron-tailored booster (mRNA-1273.529) to create bivalent vaccine, 1273.211 [16]. It generates a modestly higher level of antibody response against multiple SARS-CoV-2 Omicron subvariants (approximately 1.6-1.9 times) including BA.1 and BA.4/BA.5, and a similar antibody response against the original virus, compared to Moderna's original booster vaccine [44]. Pfizer's Omicron formula has shown substantially higher neutralizing antibody responses against Omicron BA.1.35. Studies report higher neutralisation titres following a booster dose of Pfizer bivalent BA.4/5 vaccine for BA.4/5 and other sub-variants (e.g. BQ.1, XBB) compared to the Pfizer original vaccine [45, 46]. One US study showed protection against hospitalisation or death with a bivalent BA.4/5 booster (either Pfizer or Moderna) was 61.8% compared with an original booster of 24.9% [45]. Interestingly, Livzon is also developing an Omicron-tailored protein subunit vaccine (V-01-351/V-01D), though there is limited data available as it is in phase 3 trials [29]. Currently, there is no regulatory consensus on the efficacy or necessity of Omicron-specific vaccines. Early primate studies indicate that Omicron-specific boosters offer no greater protection than a 3-dose schedule of currently available vaccines [47, 48].

Pfizer/BioNTech and Moderna vaccines have strong efficacy rates of 95% in preventing severe COVID-19 [49, 50] and are globally extremely well-received due to their high safety profile [49, 50]. Other mRNA vaccines include Takeda (TAK-919), approved solely in Japan [16]. There are currently 7 mRNA vaccines in Phase III clinical trials: ARCoV (AMS, Walvax and Suzhou Abogen), ARCT-154 (Arcturus Therapeutics), PTX-COVID19-B (Providence Therapeutics), GEMCOVAC-19 (Gennova Biopharmaceuticals), CVnCoV (CureVac), SW-BIC-213 (Stemirna Therapeutics) and LVRNA009 (AIM Vaccine and Liverna Therapeutics) [29].

mRNA vaccines have a strong safety profile, with transient side effects such as redness at injection site or fatigue [49]. They face a major challenge in that they require extremely low temperatures to transport, with the prototypical Pfizer vaccine requiring an environment of −70 °C. They are a logistical challenge, especially in lower income nations [51]. Their stringent cold-chain requirements makes them an unsuitable candidate for global vaccination efforts alone [52], particularly given the importance of global vaccination to stop VOCs generation. Thus, a range of accessible vaccine technologies are needed.

Viral vector vaccines (non-replicating)

Non-replicating viral vectors stimulate both the cellular and humoral immune systems, commonly using adenoviruses [53]. They are manufactured by modifying a harmless virus to remove its replication capacity and inserting genetic material encoding the target antigen, in this case SARS-CoV-2. This modified viral vector is then grown, purified, and formulated to create the final vaccine product, which is administered intramuscularly. There are four WHO-approved vaccines: Janssen (Johnson & Johnson), Vaxzevria (Oxford/AstraZeneca) and Convidecia (Cansino) and (Covishield), though the latter 2 are far less widely used [16].

Neither 'Janssen' [54] nor 'Vaxzevria' [55] are safe for use in children as there is limited data available. 'Janssen' studies show that a second dose 2 months after the initial dose substantially increases efficacy, especially against symptomatic infections, including when caused by VOCs. Vaccine efficacy of 2 doses, 2 months apart, was 94%. In comparison, the single dose vaccine efficacy was 72% [56]. Vaxzevria has an efficacy of 74% in individuals without prior infection [55].

One notable non-replicating vaccine is the nasal spray variant of the Ad5-nCoV vaccine by CanSino and the Beijing Institute of Technology (currently in phase IV trials). No aerosol vaccines have been approved, but early studies show promising immunogenic responses from a simple, painless, and widely-tolerated process [57]. Unlike intramuscular administration, nasal inhalation provides better respiratory mucosal immunity, while offering similar immune responses in the blood. One aerosol-delivered Ad-vectored tuberculosis vaccine significantly increased airway-tissue resident memory cells (CD4 and CD8) [58] and Ag85A-specific T cell responses in the blood [58] A second Ad-vectored intranasal vaccine was tested on mice expressing the ACE2 receptor. A single dose induced high levels of neutralizing antibodies, prompted strong systemic and mucosal immunoglobulin A (IgA) and T cell responses and almost entirely prevented SARS-CoV-2 infection in the upper and lower respiratory tracts [59]. These findings are particularly potent given that Omicron replicates significantly more quickly in human nasal epithelial cells and broader respiratory epithelial cells than the Delta variant, contributing to transmissibility [60].

These vaccines pose a challenge as subsequent/booster vaccines can result in immunity to the vector virus, while pre-existing immunity can neutralize the initial vaccine. For example, an adenovirus type-5 vectored vaccine trialled in China induced a stronger response for younger people than for those aged 55 years or older, who already had higher baseline neutralizing antibody to adenovirus type-5 [53]. To combat this baseline immunity problem, Oxford/AstraZeneca used a modified chimpanzee adenovirus, ChAdOx1, in their nCoV-19 vaccine [61]. Russia's Gameleya Research Institute used both Ad26 (also in the 'Janssen' vaccine) and Ad5 in their Sputnik V vaccine, finding an efficacy of 91.6% [62].

AstraZeneca/Oxford and Johnson & Johnson vaccines have raised concerns due to rare thrombotic adverse reactions, but multiple advisory boards have deemed these vaccines safe with benefits outweighing any risks [63, 64]. The mechanism behind vaccine-induced blood clotting is currently unknown, although unintended splice protein variants may play a role. Transcription of S protein variants may enable binding to ACE-2 expressing endothelial cells in blood vessels [65]. Some national governments (e.g. Denmark) ceased use, and there has been a broader loss of public trust [52]. Modifying the spike protein open reading frame to avoid these spike protein variants may increase vaccine safety and restore public trust [65].

Inactivated Vaccines

Inactivated vaccines are one of the most common immunization methods [66]. They are manufactured by growing the target microorganism, SARS-CoV-2, in large quantities under controlled laboratory conditions. The microorganism is then treated with chemicals, heat, or radiation to render it inactive while maintaining its structural integrity, before being administered intramuscular. There are three WHO-approved inactivated vaccines: Covaxin (Bharat), Covilo (Sinopharm Beijing) and Coronavac (SinoVac) [16]. There are 12 vaccines approved in a limited number of countries undergoing clinical trials [29].

Inactivated vaccines are well-established in the COVID-19 vaccine landscape (27% of WHO approved vaccines and 13% of candidate vaccines in clinical trials [29]); however, there are concerns around waning immunity and the need for additional vaccine doses to maintain protection. COVID-19 immunity can

wane relatively quickly following a genuine infection: researchers following recovered SARS-CoV-1 patients for 3 years found that immunity dropped significantly within 18 months [67]. The first inactivated COVID-19 vaccine, 'CoronaVac' was developed by SinoVac from July 2020 and received WHO EUL approval on June 1, 2021 [16]. However, concerns around CoronaVac's lasting immunity, particularly in the immunocompromised, led WHO to formally recommend booster programs for 'CoronaVac' [68].

Studies show that mRNA vaccines and the Novavax protein subunit vaccine elicit stronger antibody responses than inactivated viral vaccines and viral vector vaccines [67, 69]. Inactivated viruses take longer to develop and may be more suitable for booster vaccinations or as the final vaccine after an mRNA vaccine has primed the immune system [52]. Heterologous vaccination schemes have proven to be as effective as a full mRNA program and provide strong humoral/cellular immune responses [70, 71], suggesting this mosaic approach may be useful where vaccine supply is scarce.

Protein Subunit Vaccines

Protein subunit vaccines contain specific isolated virus proteins so have a strong safety profile. They are produced by selecting the specific proteins from the virus that can elicit a potent immune response. These proteins are then manufactured using recombinant DNA technology or protein expression systems and formulated into a vaccine to stimulate an immune response against the virus, before being administered intramuscularly. There are 59 protein subunit vaccine candidates and 18 approved in various countries [16]. Novavax and COVOVAX (Novavax formulation) are the only WHO-approved vaccines of this type [16].

Novavax is not recommended for children under 12, while very rare serious adverse events of myocarditis and pericarditis have been observed, though cases typically occurred within a few days after vaccination [72].

Novavax's NVX-CoV2373 vaccine is the most developed protein subunit vaccine [{, #106}73], with approval in 40 countries and efficacy of 89.7% [74]. Approved by WHO under an EUL on 21 December, 2021 [75], this vaccine showed a higher efficacy than the AstraZeneca adenoviral vaccine. Novavax has shown an efficacy of 96.4% against non-B.1.1.7 strains, higher than Pfizer's BNT161b2 (95%) and Moderna's mRNA-1273 (94.1%) [74]. However, against the B.1.351 (Beta) strain efficacy was limited at 51%. When comparing efficacy and neutralizing antibodies *in vivo*, the Novavax protein subunit vaccine gives a more robust response than viral vector and inactivated vaccines [67, 69].

Novavax is relatively simple to store and transport with a shelf life of 9 months at 2 to 8°C [76]. Given its extremely high efficacy in comparison to other vaccine types and its ease of transport, particularly in the context of Pfizer's extremely low temperature requirements, protein subunit vaccines have excelled in the vaccine space.

Viral Vector Vaccines (Replicating) and Live Attenuated Vaccines

Replicating viral vector vaccines use a modified virus as a delivery system to produce viral antigens within cells, without replicating the target pathogen. Live-attenuated vaccines (LAV) use a live, weakened form of the target pathogen, providing strong immune protection [77]. There are currently no WHO-approved replicating viral vector or live-attenuated vaccines [16], though both have candidates up to phase III trials [29].

Replicating viral vector vaccines stimulate a comprehensive immune response [66].{Malkevitch, 2004 #160} They mimic natural infection through *in vivo* replication, with natural direction caused by cell/tissue tropism [78]. Adenoviruses have been the preferred vector for SARS-CoV-2 vaccines, such as AstraZeneca, because of their high mucosal tropism [79]. The 'authenticity' in replicating vaccine infections is concerning for immunocompromised patients. Live-attenuated vaccines pose an even greater risk due to their potential to cause disease, while also being time-intensive to develop [52].

There are two replicating viral vector vaccines in phase III trials. The first (IIBR-100) uses recombinant vesicular stomatitis virus as its vector (rVSV-SARS-CoV-2-S) and is produced by the Israel Institute for Biological Research [80]. The second is aerosol based and uses influenza as its vector. DelNS1-2019-nCoV-RBD-OPT1 is produced by the University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy [81]. Intranasal vaccines show promise for respiratory tract viruses, mainly in animal trials for SARS-CoV-1, SARS-CoV-2 and MERS-CoV [59]. Both candidate vaccines use well-tolerated viruses employed successfully in previous vaccination programs [66].

There is two live-attenuated vaccine in trials. COVI-VAC by Codagenix Inc is as a single-dose intranasal vaccine with immunity against all SARS-CoV-2 proteins, making it useful against multiple strains [82]. It has progressed to phase III trials [29]. The other vaccine under development is MV-014-212 (RSV) by Meissa Vaccines. Like COVI-VAC, RSV is an intranasal vaccine that blocks infections through mucosal antibodies. Phase I clinical trial results show a strong mucosal IgA immune response preventing respiratory tract infection [83].

Treatment and Management

Repurposing Drugs

Ongoing clinical trials are assessing the treatment efficacy of pre-existing drug therapies for SARS-CoV-2, including antiviral, antiparasitic and antibiotic candidates. The following overview of these candidates is based on therapeutic utility for SARS-CoV-2, sample size and accessibility of their clinical trials and results, and their status as recommended, novel or controversial treatments.

Figure 5 explains the mechanisms of selected repurposed drugs. *(Table S2 summaries the selected repurposed drug used against SARS-CoV-2, in Supplementary Materials)*

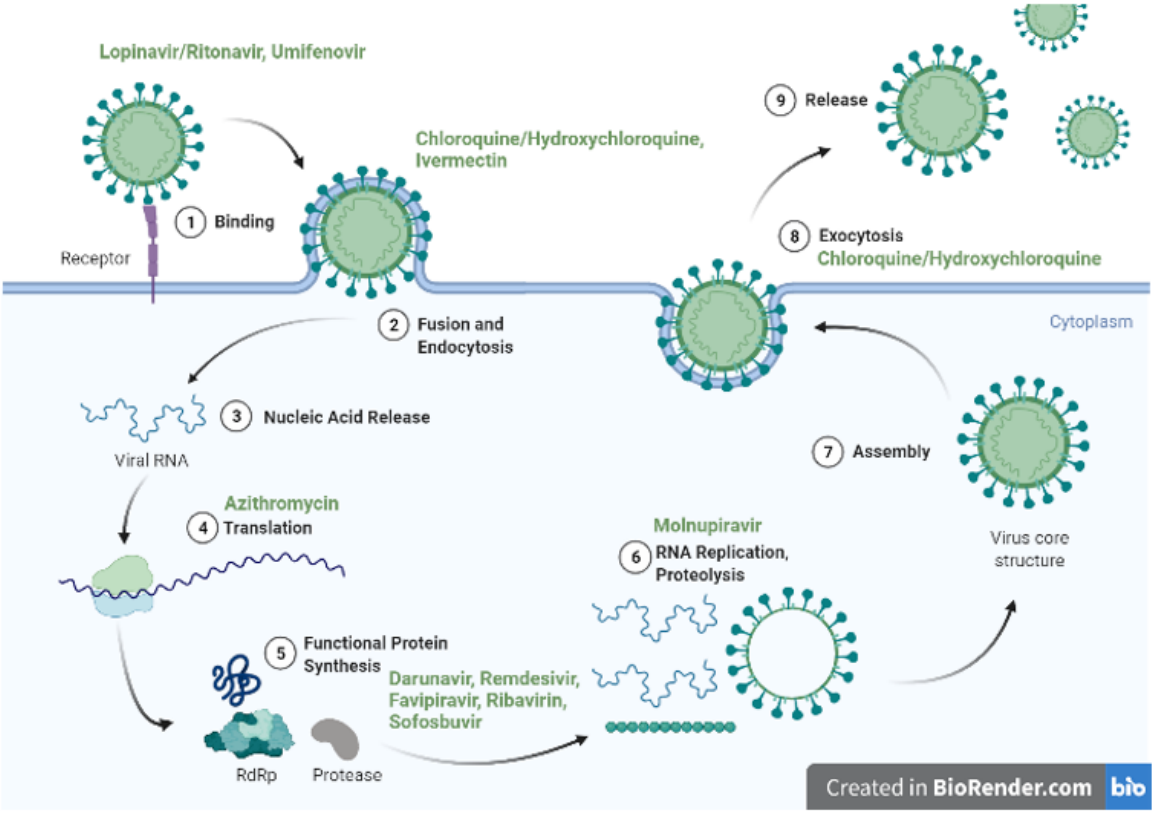

Figure 5: Simplified Viral Mechanisms and Intervention of Selected Drugs. *Graphic made with BioRender.com*. (1) SARS-CoV-2 enters the cell via binding of its spike proteins with the host cellular ACE2 receptor. Lopinavir-Ritonavir, and Umifenovir (Arbidol) act to inhibit the early stage of viral pathogenesis. (2) Fusion and endocytosis of the virus is aided by a low endosomal pH, therefore disruption of this acidic environment by Chloroquine/Hydroxychloroquine can create an antiviral effect. Ivermectin is hypothesized to inhibit viral nucleic transport. (3, 4) Viral RNA is released into the cytoplasm and translated by host ribosomal mechanisms. Azithromycin inhibits bacterial protein synthesis, however, may only serve as an anti-inflammatory for COVID-19. (5) Functional, non-structural proteins such as RNA dependent RNA polymerase (RdRp) and viral protease are synthesized. Inhibition of these proteins by Darunavir, Remdesivir, Favipiravir, Ribavirin and Sofosbuvir prevents viral RNA replication and further protein synthesis. (6) Functional proteins enable replication, transcription, and translation of SARS-CoV-2, creating structural proteins. Molnupiravir creates defective RNA nucleosides which then cannot be used to make new viruses. (7, 8, 9) Assembly and packaging of proteins make intact virions which are then released from the cell via exocytosis which can potentially be inhibited by Chloroquine/Hydroxychloroquine [17, 105, 106].

Drug	Classification	Mechanism of Action	Clinical Trial Progress	Reference
Chloroquine/ Hydroxychloroquine	Antimalarial	Alters endosomal pH	Phase IV (Recruiting)	S12
Lopinavir/Ritonavir	Antiviral	Protease inhibitor	Phase II	S13,S14
Umifenovir (Arbidol)	Antiviral	Protease inhibitor	Phase IV	S15,S16
Darunavir	Antiviral	Protease inhibitor	Phase IV	S17
Remdesivir	Antiviral	Nucleotide Analogue	Phase III	S18-S23

Favipiravir	Antiviral	Nucleotide Analogue	Phase III	S24
Ribavirin	Antiviral	Nucleotide Analogue	Phase II	S14
Sofosbuvir	Antiviral	Nucleotide Analogue	Phase IV	S25,S26
Molnupiravir	Antiviral	Nucleotide Analogue	Phase II/III	S27-S31
Ivermectin	Antiparasitic	Inhibits viral entry, anti-inflammatory	Phase III	S32-S33
Azithromycin	Antibiotic	Inhibits bacterial protein synthesis, anti-inflammatory	Phase III	S34,S35

Table S2: A summary of selected repurposed drugs used against SARS-CoV-2.

Remdesivir

Remdesivir (VEKLURY®) is an antiviral prodrug initially developed to treat RNA viruses, such as Ebola [107], and the first drug approved by the U.S. Food and Drug Administration (FDA) for SARS-CoV-2 [108]. Remdesivir is a broad-spectrum antiviral that was applied to SARS-CoV-2 given its success with previous coronaviruses. An adenosine nucleotide, it works by being metabolized into remdesivir triphosphate (RDV-TP) [109]. RDV-TP is a highly selective (3.65-fold) competitive inhibitor of adenosine triphosphate (ATP). It targets the RNA-dependent RNA polymerase (RdRp) enzyme of the SARS-CoV-2 virus, incorporating itself into the viral RNA chain during replication to prevent addition of further nucleotides.

Side-effects for Remdesivir are typically mild, but RDV-TP also affects DNA and RNA polymerases in humans which risk injuries to organs. Intravenously administered Remdesivir may cause elevated liver enzymes, harmful for patients with liver conditions [110]. It may be used in renally-impaired patients with estimated globular filtration rates (eGFR) < 30 ml/min [111].

Both placebo and standard of care (SOC) trials show promising results. A 10 day Remdesivir treatment reduced median recovery time from 15 to 10 days in severely ill patients [112]. At the end of the trial, 46% of Remdesivir patients were not hospitalized compared to 36% of placebo. In SOC comparisons, patients treated with Remdesivir for 5 days showed significant improvement over SOC patients on Day 11, with 70% of Remdesivir patients not hospitalized compared to 60% of SOC [113, 114]. One significant trial measured the clinical status of outpatients at 28 Days, comparing a 3-day treatment to placebo [115]. 0.7% of Remdesivir patients had COVID-19, related hospitalizations or all-cause deaths compared to 5.4% of placebo. Remdesivir treatment reduced the rate of hospitalization or death due to COVID-19 by 87% [116].

Aerosolized nano-liposomal carriers of Remdesivir may improve direct drug delivering to lung cells, increase metabolization to RDV-TP and reduce side-effects [117]. Remdesivir nanoliposomes had minimal cytotoxicity in A549 lung carcinoma cells, sustained release up to 50 hours, and significant lung deposition [118]. This aerosol delivery is a future avenue for greater efficacy and self-administration.

Molnupiravir

Molnupiravir (EIDD-2801/MK-4482/Lagevrio®) is a wide-spectrum antiviral prodrug, originally tested against influenza A [119]. The FDA gave an EUA for Molnupiravir in December 2021 [120]. Molnupiravir is metabolized into the active form β-d-N4-hydroxycytidine (NHC) triphosphate, leading to mutated RNA products [121]. In SARS-CoV-2, NHC triphosphate is incorporated into the RNA chain, where it induces errors in replication and mutations in the viral genome, limiting replication and spread.

Molnupiravir side effects include gastro-intestinal symptoms, dizziness and nausea. It has a clean safety profile in general [122, 123]. Molnupiravir has been found to significantly reduce SARS-CoV-2 load and disease transmission in ferret models [124]. In humans, a phase I trial found no significant increase in adverse effects compared to placebo [122, 123]. A phase II trial in hospitalized patients compared the efficacy of placebo treatment and 200 mg, 400 mg, and 800 mg dosages of Molnupiravir twice per day for a 5-day course [125, 126]. The trial found no significant increase in adverse effects, median recovery or all-cause mortality with higher dosages.

A phase III trial found that Molnupiravir (800mg over a 5-day course) significantly reduced percentage of all-cause hospitalization or death (7.3%) compared to placebo (14.1%) to placebo in non-hospitalized, non-vaccinated participants with mild-moderate COVID-19 [127, 128]. Treatment reduced risk of hospitalization or death by 31% compared to placebo.

Favipiravir

Favipiravir (Avigan®) is an broad-class antiviral initially approved for novel influenza [129]. *In vitro* and *in vivo s*tudies demonstrate its efficacy against Ebola, arenavirus, yellow fever virus and foot-and-mouth disease [130]. Favipiravir-RTP, the active form of this drug (a purine analogue), acts as a substrate for the viral RdRp, inhibiting its activity and ultimately terminating

protein synthesis [130, 131]. Just like with other viruses, for SARS-CoV-2 it hinders replication of the virus and thus viral load in the patient.

Favipiravir has no optimal dosage established for SARS-CoV-2 [130]. It's oral administration allows for easy at-home treatment of mild-to-moderate COVID-19 [132]. Side effects are mild, including nausea, vomiting, diarrhea and reversible elevation of bilirubin and uric acid. Favipiravir is teratogenic so not administered to pregnant patients [130].

The limited Favipiravir trials for SARS-CoV-2 treatment show reasonable efficacy. One phase III trial showed reduction in median time to clinical cure from 5 to 3 days [133]. In a second trial, by day 10 98% of patients, compared to79% of control, returned negative PCR testing [134].

Ivermectin

Ivermectin (Stromectol®) is an antiparasitic, semisynthetic, anthelmintic agent with potent antiviral and anti-inflammatory properties. Derived from the soil bacterium *Streptomyces avermitilis*, it was originally used in animals for heartworm and parasites. It is WHO-approved for human treatment of river blindness, scabies and lice [135]. Ivermectin shows antiviral activity against a range of RNA and some DNA viruses, including Zika, dengue and yellow fever [136], though its exact mechanism is unclear. In parasites, ivermectin selectively binds to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells, resulting in hyperpolarization and paralyzing the parasite. In viruses, it may have antiviral action via inhibition of IMPα/β1-mediated nuclear import of viral proteins into host cells [136]. By disrupting this process, it may impede the virus' ability to replicate and spread in the body.

Potential side effects including headache, muscle pain, or nausea [135, 137], as well as sudden drop in blood pressure and facial/limb swelling [138]. Laboratory test abnormalities include decrease in white cell count and elevated liver tests [138].

In vitro studies show that SARS-CoV-2 infected cells treated with 5 μM of Ivermectin result in a 99.98% reduction in viral RNA [137]. In a phase III trial, patients treated with Doxycycline and Ivermectin recovered more quickly (60.7% *vs.* 44.4%), were less likely to progress to more serious disease (8.7% *vs.* 17.8%), and were more likely to be COVID-19 negative by PCR on day 14 (7.7% *vs.* 20.0%) [139]. Also, topical Ivermectin and Carrageenan prevented COVID-19 spread in an observational trial, with 0% positive cases after 28 days compared to 11.2% in the control [140].

Following a trend of patients self-administering Ivermectin, the FDA advised against its usage and restricted prescriptions by general practitioners. Serious harm may occur in self-medicating without proper guidance [138]. However, reliable results from ongoing trials could lead to its repurposing in combination with other therapeutics for COVID-19 treatment, potentially changing public perception and usage.

Paxlovid

Pfizer's Paxlovid was the first oral antiviral to receive an EUA, approved by the FDA in December 2021 [141]. It contains nirmatrelvir and ritonavir, co-packaged for oral use. Nirmatrelvir is a SARS-CoV-2 main proteases inhibitor, designed especially for SARS-CoV-2, which prevents the protease from cleaving viral polyproteins into functional components necessary for viral replication. Ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor, originally designed for treatment of HIV/AIDS. In Paxlovid, it increases the concentration and duration of nirmatrelvir in the body by inhibiting the enzyme responsible for metabolizing nirmatrelvir. Together, the two drugs work toward reducing viral replication and therefore viral load in patients. Side effects are typically mild, including nausea, fatigue and altered taste [142].

Treating high-risk patients with only nirmatrelvir showed a 67% reduction in hospitalizations and an 81% reduction in mortality in patients 65 years and above. No significant benefit in protection from severe COVID-19 was seen in younger adults [143]. Early administration of Paxlovid significant reduces risk of all-cause mortality and disease progression, and reduces viral burden faster than non-use [144]. A 2023 US study found that high-risk patients receiving Paxlovid within five days of a positive COVID-19 test had 26% lower risk of long COVID symptoms after 90 days compared to placebo [145]. It was initially aimed at those with moderate COVID-19 at extreme risk of severe disease progression [142], but is now indicated for non-hospitalized patients at risk of disease progression [144].

Immunotherapies

Monoclonal Antibodies

There are three main recombinant monoclonal antibodies (rMABs): Casirivimab/Imdevimab, Bamlanivimab/Etesevimab and Sotrovimab. The three rMABs therapies work in a similar manner, reducing a patient's viral load to accelerate recovery. *(Figure S3 explaining on neutralization of virus via monoclonal antibodies, in Supplementary Materials)*

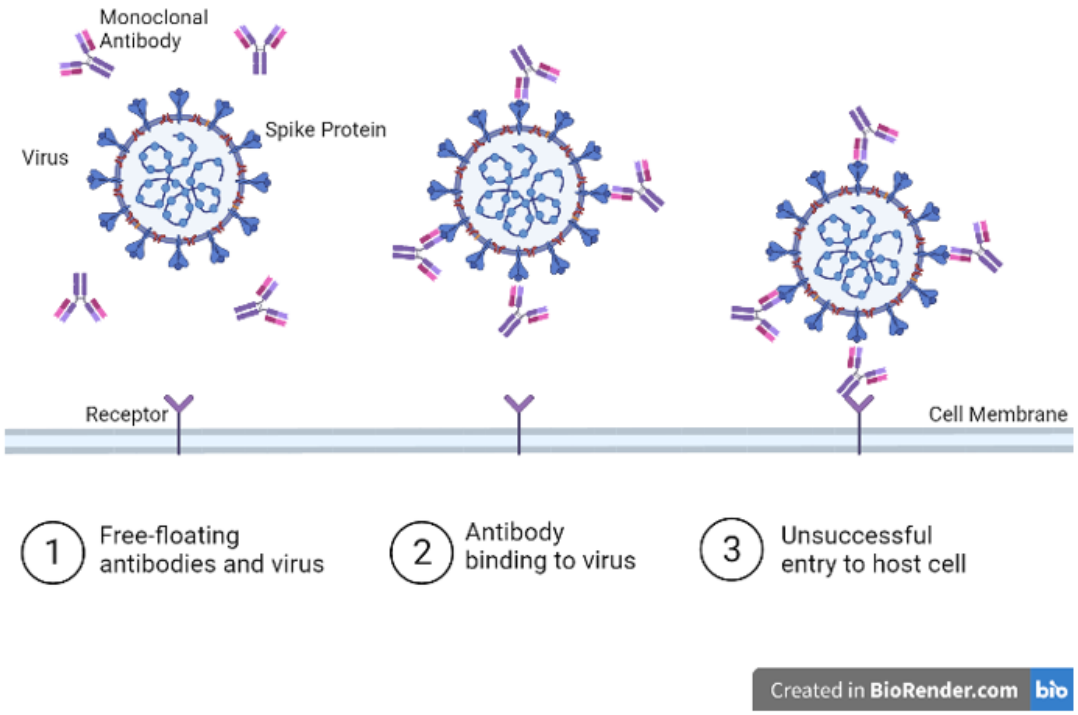

Figure S3: Neutralization of virus via monoclonal antibodies. When monoclonal antibodies are present, they attach to the spike protein of the virus, preventing them from binding to the receptor on the host cell, thus endocytosis is blocked, and the virus can no longer replicate in the cell. *Graphic made with Biorender.com.*

Casirivimab/Imdevimab is a combination of rMABs, sold under the name REGEN-COV™ or Ronapreve™. Both Casirivimab and Imdevimab are immunoglobulin gamma-1 proteins which attach to the spike protein of SARS-CoV-2 [146]. REGEN-COV™ is effective as both a preventative measure and a treatment. Of patients who had never been infected with SARS-CoV-2, 4.8% of a REGEN-COV™ treatment group developed COVID-19 after a 4 week period in comparison to 14.2% of the placebo [147]. As a treatment, REGEN-COV™ significantly reduces hospitalization and death due to COVID-19 and results in a shorter recovery period (10 days compared to 14 days for placebo) [148]. REGEN-COV™ is promising for both treating and preventing COVID-19 and could be an alternative to vaccination for immunocompromised and other unvaccinated people.

Bamlanivimab/Etesevimab are similar rMABs which neutralize the virus, prevent binding to ACE2 receptors and entry to host cells (Graphic representation found in appendix under Figure 8 and 9) [149, 150]. Bamlanivimab/Etesevimab has reduced hospitalization and death by COVID-19 [151]. After 28 days, hospitalization was 2.1% in treatment group vs. 7.0% in placebo. 10 deaths occurred in placebo, while the treatment group also showed lower rates of high viral load (9.8% vs 29.5% in the placebo group). Bamlanivimab/Etesevimab reduced viral load but not recovery time, suggesting need for further research and trials.

Sotrovimab is another rMAB that was originally used against SARS-CoV-1 as well as other sarbecoviruses [152]. It binds to a highly conserved epitope of the SARS-CoV-2 spike protein. Sotrovimab contains two modifications in the Fc binding region to increase its half-life, therapeutic duration and concentration [153]. Sotrovimab shows promising trial results with hospitalization rates of 1% in the treatment group compared to 7% in placebo. Only 2% of the treatment group experienced serious adverse effects compared to 6% of placebo [152]. Sotrovimab shows promising results as broader therapy for all sarbecoviruses including SARS-CoV-2.

Convalescent Plasma Therapy

Convalescent plasma (CP) therapy was recommended as a possible treatment early in the pandemic due to its antiviral properties and success in prior infection outbreaks, endemic situations like SARS-CoV-1, H1N1, and Ebola, when treatments were scarce [154]. The antibodies present in convalescent plasma, taken from a recovered patient for the target virus, recognize and bind to specific viral components, neutralizing the virus and triggering an immune response. Enhancing the antiviral response and reducing hyperinflammation are key in treating COVID-19

[21]. CP from recovered COVID-19 patients contains neutralizing IgM and IgG antibodies which limit viral growth [21]. It also encompasses immune-modulatory cytokines that regulate the cytokine storm.

The FDA authorized CP therapy for emergency use and allowed the use of high-titre COVID-19 CP based on a large observational study of hospitalized patients, which showed that the risk of death was 7% lower in a high-titre CP infusion subgroup compared to a low-titre group [155].

CP trials have yielded mixed results, due to factors such as therapy commencement, the quality and number of antibodies transfused, and donor characteristics. To properly select an appropriate donor, conduct serological tests via ELISA prior to trial to measure spike and RBD specific antibody present in the serum. The functionality and quality of these antibodies should be ascertained by neutralization assays [156].

The RECOVERY trial tested CP efficacy in patients that entered the hospital with COVID-19. CP had no influence on length of hospital stay while 24% of both groups died within 28 days. Thus, the largest clinical trials for CP concluded that high-titre CP was ineffective in improving survival or other clinical outcomes [157]. A Bayesian re-evaluation of the RECOVERY trial found that the subgroup of patients who had not yet developed anti-COVID-19 antibodies benefited from CP [158]. This was supported by a randomized, placebo-controlled trial of CP with high IgG titres given within 72 hours of mild symptoms onset. 3% of CP patients developed serious respiratory disease compared to 16% of placebo [159].

The PLACID trial had multiple limitations including bias due to its open label design and no pre-commencement computation of neutralizing antibody titre in donors and patients. It found that CP did not alleviate development of severe COVID-19 nor all deaths.

CP should clinically benefit COVID-19 patients; however, trials have yielded heterogenous results in reducing mortality and clinical improvement. Most CP data originates from uncontrolled cohort studies or case series, thus more controlled studies are needed.

CRISPR/Cas Technology for Elimination and Treatment

As various vaccine platforms were being developed and refined as preventive measures, other biotechnological tools to eliminate the virus were explored, with CRISPR on the forefront. The gene-editing technology, CRISPR/Cas showed promise *in vitro and in vivo* models, in preventing viral replication of SARS-CoV-2 due to its high precision nature and versatility. Previous successful reprogramming of CRISPR-Cas13 to detect and inhibit RNA viruses suggest its potential against any virus, as demonstrated in studies performed by the Broad Institute (MIT) and Harvard University [160].

Reprogrammed CRISPR-Cas systems have shown promise in silencing the efficiency of SARS-CoV-2 [161]. Accessible regions of spike and nucleocapsid transcripts were targeted to suppress replication-component SARS-CoV-2 in Green African monkey kidney cells and human embryonic kidney cells, achieving levels of up to 95% efficiency. The CRISPR-Cas system also inhibited nucleocapsid expression of the virus by 90% for both the ancestral virus and the Delta variant, achieved through CRISPR RNA (crRNA) redesign.

Furthermore, Prophylactic Antiviral CRISPR in huMAN cells (PAC-MAN) effectively degrades SARS-CoV-2 sequences in human lung epithelial cells [26]. This system uses repurposed Cas13d RNA-guided RNA endonuclease activity to target and inhibit viral replication by targeting specific genomic regions such as the RNA-dependent RNA polymerase (RdRP) and nucleocapsid proteins, which would halt viral replication.

CRISPR technology's adaptability enables rapid cRNA design and production, making it extremely adaptable to ongoing SARS-CoV-2 mutations. PAC-MAN's RNA-targeting approach suggests potential efficacy against all coronavirus strains. However, the success of CRISPR therapeutics depends on effective delivery to infected cells and minimizing off-target expression and cleavage in the host.

CRISPR-based Diagnosis

Fast and accurate diagnostics are crucial to controlling transmission of SARS-CoV-2. PCR testing, while accurate, can take up to 72 hours for result. Rapid antigen tests give results in 15 to 20 minutes but are less accurate and susceptible to user errors and inaccuracies [162] CRISPR-based assays for SARS-CoV-2 detection can take only 40 minutes while maintaining accuracy [163].

There are two main CRISPR-based diagnosis tools: DNA endonuclease-targeted CRISPR trans reporter (DETECTR), and STOPCovid (SHERLOCK Testing in One Pot) detection. DETECTR (Mammoth Biosciences) was first showcased in 2017, followed by SHERLOCK (SHERLOCK Biosciences) in 2018 [164].

DETECTR is a CRISPR/Cas12 based detection technique utilizing a lateral flow assay. For a COVID-positive patient, Cas12 accurately targets and cleaves a reporting molecule confirming the virus' presence in the cell (Figure 6). This technology has several advantages over current PCR testing: rapid results, no need for intricate laboratory infrastructure, and the integration of simple, accessible reporting formats. CRISPR diagnosis is a cheaper, quicker option for viral detection [163]. The SHERLOCK (STOPCovid) test provides accurate results in under an hour with only two key steps: liquid handling and tube opening [165]. This makes testing simpler and decreases sample cross-contamination. Clinical trials show extremely high accuracy for both negative and

positive detection [163]. American trials involved 12 SARS-CoV-2 positive and 5 negative patients. Results successfully revealed SARS-CoV-2 detection in 3/3 trials for 11/12 patient samples with only one misrepresented answer in the three rounds. In negative patients, STOPCovid accurately provided negative results [165].

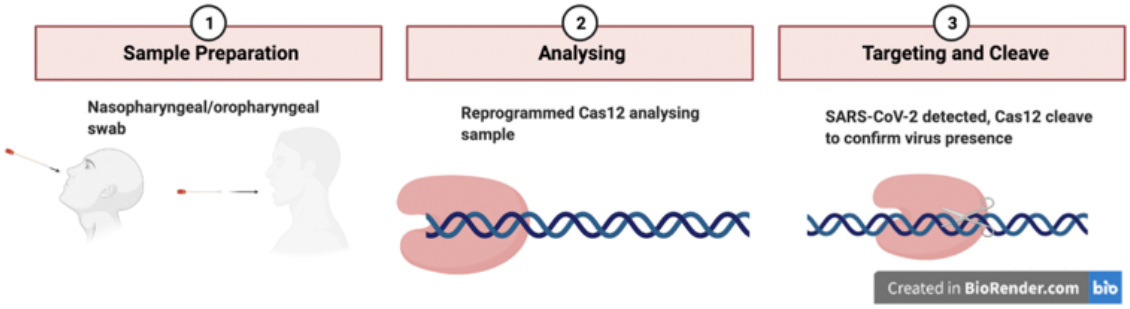

Figure 6: The SARS-CoV-2 DECTECTR diagnosis technique using CRISPR-Cas-12 Adapted from "COVID-19 Diagnostic Test through RT-PCR", *Graphic made with BioRender.com.*

In May 2020, SHERLOCK became the first CRISPR SARS-CoV-2 rapid diagnostic tool approved by the FDA [166], followed by Mammoth Bioscience's DETECTR in August. These diagnostic tools outweigh all current competitors in SARS-CoV-2 detection. They will only be refined to be more cost-effective and accurate. Indeed, on January 21st 2022, Mammoth Bioscience's high-throughput assay, DETECTR Boost, was given emergency approval for laboratory use [167]. In January 2022, pharmaceutical giant Bayer paid Mammoth Biosciences $US 40 million to work on gene-editing technologies in four different diseases using their extensive CRISPR toolbox [168]. SARS-CoV-2 technologies based on alternative CRISPR-Cas systems are likely to lead to new and improved methods for diagnosis, treatment and prevention.

Conclusions

Global case numbers of SARS-CoV-2 infections have passed 765 million as recorded in May 2023. The rapid advances in biotechnology during the pandemic has shown the power of global medical cooperation in combating SARS-CoV-2. Among the available treatment and management regiments, vaccination platforms such as mRNA, as well as pre-existing viral vectors, and inactivated vaccines were the best defence against severe illness and death caused by SARS-CoV-2 pandemic. Due to the ease of production and enormous efficacy, mRNA vaccines have been heralded as the future of vaccine technology. The success of mRNA platform in preventing the SARS-CoV-2 infection have led to further explorations and development of mRNA vaccines for other infectious diseases as well as cancer. Furthermore, in tandem with development of vaccine platforms, there is hope for alternative ways of administration of vaccines, transitioning from intramuscular (IM) to the non-invasive intranasal, which may ally fears for many. Unfortunately, at this time, only the viral-replicating platforms are using this approach in clinical trials.

At the height of the pandemic, while waiting for EUA and large-scale production of the various vaccines, healthcare returned to basics in treatment and management, that is, utilizing repurposed medications and monoclonal therapies. Most of these broad-class drugs were able to manage mild to moderate symptoms of SARS-CoV-2 at home; however, combinatory use with immunotherapies improved their therapeutic efficacy. On the other hand, convalescent plasma may have potential but presented logistical challenges and mixed results. Nevertheless, due to limited resources, infrastructure, and economics, not all were privy to these treatments.

Aside from the refinement of various vaccines platforms, one of the most significant biotechnological breakthroughs lie in the redesigning of CRISPR-technology for both detection and treatment purposes. Repurposing of CRISPR technology such as PAC-MAN would represent an additional treatment for combatting mutating variants. Current mRNA vaccines together with putative CRISPR technology, we should be able to mount an agile response not only to coronaviruses, but to other future viral threats. The remarkable scale of global cooperation seen during the SARS-CoV-2 pandemic has reduced vast human suffering and mortality. Furthermore, biotechnological breakthroughs will continue to evolve, thus preparing us for the future pandemics.

Disclosure

Author Contributions: Conceptualization, B.Y.C. and C.Y.W.; methodology, B.Y.C. C.Y.W. and C.S.; software, S.P.T.; validation, B.Y.C. C.Y.W. and C.S.; formal analysis, S.P.T., P.E.B., A.B., A.H., V.N. and A.S.; investigation, S.P.T., P.E.B., A.B., A.H., V.N. and A.S.; resources, S.P.T., P.E.B., A.B., A.H., V.N. and A.S.; data curation, B.Y.C. and C.Y.W.; writing—original draft preparation, S.P.T., P.E.B., A.B., A.H., V.N. and A.S.; writing—review and editing, S.P.T, B.Y.C and C.Y.W.; supervision, B.Y.C. C.Y.W. and C.S. All authors have read and agreed to the published version of the manuscript

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S15. Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus. https://ClinicalTrials.gov/show/NCT04260594

S16. A Prospective/Retrospective,Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia. https://ClinicalTrials.gov/show/NCT04255017

S17. Darunavir/Cobicistat vs. Lopinavir/Ritonavir in COVID-19 Pneumonia in Qatar. https://ClinicalTrials.gov/show/NCT04425382

S18. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19). https://ClinicalTrials.gov/show/NCT04292899

S19. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment. https://ClinicalTrials.gov/show/NCT04292730

S20. Study to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of Coronavirus Disease 2019 (COVID-19) in an Outpatient Setting. https://ClinicalTrials.gov/show/NCT04501952

S21. Adaptive COVID-19 Treatment Trial 2 (ACTT-2). https://ClinicalTrials.gov/show/NCT04401579

S22. Adaptive COVID-19 Treatment Trial (ACTT). https://ClinicalTrials.gov/show/NCT04280705

S23. Adaptive COVID-19 Treatment Trial 3 (ACTT-3). https://ClinicalTrials.gov/show/NCT04492475

S24. Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19. https://ClinicalTrials.gov/show/NCT04542694

S25. Evaluation of Sofosbuvir and Daclatasvir Combo in COIVD-19 Patients in Egypt. https://ClinicalTrials.gov/show/NCT04773756

S26. Sofosbuvir/Ledipasvir and Nitazoxanide for Treatment of COVID-19. https://ClinicalTrials.gov/show/NCT04498936

S27. Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002). https://ClinicalTrials.gov/show/NCT04575597

S28. Study of MK-4482 for Prevention of Coronavirus Disease 2019 (COVID-19) in Adults (MK-4482-013). https://ClinicalTrials.gov/show/NCT04939428

S29. The Safety of Molnupiravir (EIDD-2801) and Its Effect on Viral Shedding of SARS-CoV-2 (END-COVID). https://ClinicalTrials.gov/show/NCT04405739

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S31. Efficacy and Safety of Molnupiravir (MK-4482) in Hospitalized Adult Participants With COVID-19 (MK-4482-001). https://ClinicalTrials.gov/show/NCT04575584

S32. Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection. https://ClinicalTrials.gov/show/NCT04523831

S33. USEFULNESS of Topic Ivermectin and Carrageenan to Prevent Contagion of Covid 19. https://ClinicalTrials.gov/show/NCT04425850

S34. A Multicentre Open-label Two-arm Randomised Superiority Clinical Trial of Azithromycin Versus Usual Care In Ambulatory COVID19 (ATOMIC2). https://ClinicalTrials.gov/show/NCT04381962

S35. Hydroxychloroquine vs. Azithromycin for Outpatients in Utah With COVID-19. https://ClinicalTrials.gov/show/NCT04334382.