Rethinking Our COVID-19 Strategy

Samuel Brauer, Ph.D.

Nanotech Plus, LLC, Shelton, CT 06484, USA

www.nanotechplus.net

Submitted: February 18, 2021

Accepted: March 15, 2021

Published: March 18, 2021

Abstract

As of Feb 21, 2021, the COVID-19 pandemic claimed over half a million lives in the U.S., and over half of the country's population likely had an infection. Our strategy to deal with the COVID-19 pandemic to date has been to rely very heavily on vaccination while testing and antiviral development was given short shrift. Initial results of vaccines appeared promising, but there have been increased numbers of new variants than expected due to a high effective mutation rate. These new variants show the strong possibility of mutational escape from existing antibodies, whether these antibodies are generated from natural infection or a vaccine. Increasing infection rates in the UK and Manaus, Brazil, has shown that even high seroprevalence from previous infection waves may not block these new variants. The development of new vaccines for COVID-19 has now become exponentially more challenging for several reasons. Given our partial success with the current vaccination strategy, it is time to revisit the idea of antiviral development combined with significantly increased testing as a means of controlling this pandemic. Only a more balanced strategy involving all available control technologies: testing, antiviral drugs, and vaccination will effectively end this pandemic.

Keywords

Covid-19, vaccination, antiviral, strategy, vaccine, therapy

Purpose and Rationale

This paper aims to stimulate discussion around our strategy for dealing with the COVID-19 pandemic and to present alternatives to our current strategy. Given the high loss of life and lack of a clear end to the pandemic, a robust discussion based on science and economic considerations is needed to ensure that we meet society's goals of reducing loss of life and returning to the pre-pandemic level of economic and social growth. It is beyond this paper's scope to deal with the current response to the COVID-19 pandemic, but there is no doubt that only a more balanced approach and the combination of prevention and treatment could speed this pandemic's end and improve our response to subsequent pandemics. We need to answer a simple question: What do we do if the vaccines fail?

Introduction

Pandemic strategies focus on controlling infection spread, whether the infectious agent is a

bacterium, fungus, or virus. The first critical task is the determination of the extent of the infection in the populace. The second critical task is to identify methods of reducing the infection's impact on society through isolation, prophylactic and therapeutic measures. For COVID-19, we are fortunate to have already developed sound biological and nanomedical science and technologies to identify infected individuals, prevent severe disease, and reduce morbidity and mortality rates in infected individuals. However, are we applying these various technologies correctly to the COVID-19 pandemic? The COVID-19 pandemic claimed over half a million lives in the U.S. as of Feb 21, 2021 [1], and over half of the country's population has likely had an infection.¹

This year, both hospitalizations and mortality were increasing at an alarming rate [2], although recently, the trends reversed.

¹ This is based on the reported number of infections, ~28 million as of Feb. 21, 2021, which when multiplied by a factor of 7 yields over 195 million infections. See below for more details.

This bit of good news should not be taken too optimistically. As of the end of February 2021, infection rates remain well above the peak infection rates of the summer of 2020, and over 2,000 people per day are succumbing to COVID-19. Unfortunately, infection rates now are rising again globally [3].

There has been relatively little debate in the scientific literature whether the path we have chosen to this point, such as heavily favoring vaccination, has been the most effective way to save lives and return to a new normalcy. At this point, there are at least two competing strategies:

1. Continue to rely on vaccination and begin developing second-generation vaccines to treat new variants as they emerge.
2. Increase testing and antiviral development and rely on isolation rather than vaccination to reduce infection rates.

Given the now clear need to develop second-generation vaccines if we are to continue down the path of trying to control COVID-19 through vaccination, it seems that vaccination alone is not the most efficient way to end this pandemic reduce the loss of life. What are our alternatives?

A prescient April 2019 review [4] by Totura and Bavari on the possibilities of a coronavirus pandemic and potential treatment options provided straightforward suggestions for a coronavirus pandemic strategy. The authors concluded that a broad-spectrum pan-coronavirus antiviral offered the best possibility of controlling a future coronavirus outbreak rather than vaccination. Conversely, pan-viral antiviral drugs' limitations were clear since these drugs were developed with safety, rather than efficacy, as the primary criterion for success [4].

To date, most antiviral drug developments focused on repurposing existing drugs rather than developing new drugs to specifically target conserved proteins of the Severe Acute Respiratory Syndrome (SARS) CoV-2 virus. Coronaviruses have evolved independently of other viruses for millions of years [5]. Since their enzymes are sufficiently different from other viruses, antivirals developed for other viruses are likely to be ineffective, as demonstrated by the failure of hydroxychloroquine, chloroquine, lopinavir, and interferon [6].

All too often, drugs repurposed for COVID-19 have had few theoretical underpinnings for their efficacy and their clinical trials have sapped resources that could have been used for more promising compounds. As of July 2020, over a dozen repurposed antiviral therapies (some drugs were being evaluated as monotherapies, while other drugs were part of a cocktail) were in clinical trials [7] although there have been no significant successes other than Remdesivir. Coupled with the well-publicized hydroxychloroquine debacle, these hastily done clinical trials [8] have reduced optimism that antiviral drugs hold much promise. Currently, there are hundreds of antiviral drugs in clinical trials in the U.S., but most of these clinical trials are too small to show significant results. The U.K. clinical trials, which employed sufficient statistical power, provided a far better approach [9].

Totura and Bavari also observed that there were two main challenges to vaccination:

1. the effective mutation rate of coronaviruses was high enough to allow mutational escape – a possibility which has become all too real [10], and
2. previous work on vaccines for SARS and Middle East Respiratory Syndrome (MERS) showed the possibility of severe side effects of coronavirus vaccines.

While SARS CoV-2 does have a lower mutation rate than influenza on a per genome replication basis [11], the widespread infection has enabled the virus to mutate much faster than expected. This enhanced mutation rate increased the possibility of mutational escape from the antibodies produced by natural infection and the antibodies produced by vaccines or antiviral drugs. Treating immunocompromised patients with convalescent plasma may have also dramatically accelerated the development of new mutations and insufficient isolation precautions have allowed these more infectious variants to escape [12].

Fortuitously, both new antiviral drugs and point of care (POC) testing products are near commercial rollout. Unfortunately, these products had limited government support to date. These new products offer an alternative to our current vaccine strategy that should be rapidly explored at this juncture.

Discussion:

Proposed Strategy:

The current COVID-19 strategy relying heavily on vaccination largely ignores other important methods of controlling pandemics, notably testing and antiviral drugs. A new strategy should strike a better balance between the following four options:

Testing

Isolation/quarantine

Vaccination

Antiviral drugs

1: Testing

The capabilities of testing to control COVID-19 infections in the populace have not been well exploited, given the current limitations of existing technologies. Most current tests for COVID-19 rely on polymerase chain reaction (PCR) testing, but the development of POC and home tests has lagged badly. We still cannot answer a simple question with any surety: How many people in the U.S. have had a COVID-19 infection since the pandemic began? The number of reported cases has been extraordinarily misleading. Although the Centers for Disease Control eventually began publishing estimates of the actual number of COVID-19 cases²³ [13, 14], the damage has been done, and the public has grown accustomed to a very inaccurate description of the pandemic.

Our reliance primarily on centralized laboratory testing has had a high cost. We cannot test enough individuals daily to identify who should self-isolate to reduce overall COVID-19 infections. At a minimum, less than one in four COVID-19 infections are reported, while the previous methodology suggested the rate was as low as one in seven, which may be more accurate. It has been estimated that nearly 60% of COVID-19 infections are due to transmission from people who don't even know they've been infected! [15] Overall, the U.S. can test about 2

million people/day [16]. This is inadequate for most pandemics as it would take ~4 months to test everyone in the country - once.

Current COVID-19 testing paradigms rely on PCR technology. While PCR is highly accurate at identifying even small amounts of the nucleic acids of the virus reliably, the process is cumbersome since it requires research instruments that were not designed for clinical use, and the technology has been challenging to scale to the requirements of the pandemic. Testing for antibodies to SARS CoV-2 to identify individuals who have previously had a natural infection has become less helpful as vaccines produce similar antibodies.

Defeating this pandemic requires testing a significant fraction of the population daily to identify and isolate infected individuals quickly. We need to scale up our testing capacity by two orders of magnitude, a requirement that was noted back in August 2020 [17]. Compared to centralized testing, POC testing offers a far better option as it can be readily scaled up to the needed volumes [18]. While POC testing is unlikely to be as accurate as PCR, the gold standard of laboratory testing, this is a situation where the perfect has become the enemy of the good, and a precise but slow method is less valuable than a rapid but less precise test [19]. A detailed review of testing options, including options for low resource countries, also concluded that POC testing was critical [20]. If we can quickly identify infected individuals- (even if not as accurate as could be done by PCR), we would still be able to end this pandemic much faster. Unfortunately, public messaging which suggests that vaccination would protect others from infection has led to an alarming drop in testing nationally, with recent (Feb 28, 2021) testing rates falling to approximately one-quarter of their peak in some cities [21].

2: Isolation/Quarantine

In the beginning, a false proposition was put forward that ending the pandemic by isolation would cause economic catastrophe. We face a

² The methodology the CDC used to calculate the estimated number of cases has changed. Prior to Jan. 2021, the methodology was to simply multiply the reported number of cases by 7x. Current methodology is shown here: www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html

³ Note that the CDC did not give an explanation for the change in methodology. This paper uses the previous methodology which was based on this paper here: <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1780/6000389>

cruel dichotomy: open the economy and accept increased fatalities or close the economy as much as possible and reduce casualties. Instead, consider the example of China, which successfully reduced the spread of infection and mortality early on with an aggressive lockdown procedure but has subsequently suffered neither the economic losses nor the human losses of the United States.

While isolation/quarantine does have a financial cost, a relatively brief lockdown period would have had a much lower economic cost and saved more lives than the dithering strategy that we employed. What is now clear is that the way to reduce this pandemic's economic costs is to end it quickly and efficiently, simultaneously saving lives and reducing suffering.

3: Vaccination

Several types of vaccines have been developed and deployed in less than a year in a remarkable achievement. This accomplishment owes a debt to the cutting-edge basic science and nanomedicine research to develop an mRNA vaccine. The ample funding thrown at the problem also reduced the risk of pharmaceutical companies.

There is no denying the previous successes of vaccines in dealing with terrible viral scourges ranging from smallpox, measles, rubella, and polio to Ebola [22] but the record of vaccines for dealing with viruses such as influenza, RSV, dengue, herpes, HIV, and other viruses is much spottier. With a much higher rate of mutation when compared with DNA viruses, RNA viruses have often managed to elude vaccines. For example, some clinical trials of HIV vaccines led to an increased risk of contracting the virus [23], while recent clinical trials of dengue vaccines [24] also failed.

Back at the beginning of the pandemic, when death tolls were in single digits, vaccination was already being seen as the only solution [25], although vaccines were not expected to be available until Fall 2021 at the earliest. Unfortunately, the virus has remained a moving target, and several variants of concern have arisen [26]. Regional variants have been difficult to track given our lack of sequencing data. In a troubling finding, a new variant that is likely to evade existing antibodies has been found in New York [27], a region that was hard hit a year ago. Essentially, the virus has mutated faster than we can get people vaccinated. Existing

vaccines that we are struggling to roll out in the winter/spring of 2021 target either the original strain, or the D614G variant which became globally dominant by June 2020 [28]. While there have been glib calls to develop second-generation vaccines [29], this is a difficult task while we still do not have enough reliable data on first-generation vaccines.

Clinical trials of COVID-19 vaccines were not designed to detect the presence or absence of sterilizing immunity; answering whether or not vaccination reduces viral transmission requires additional data. Israel immunized approximately $\frac{1}{4}$ of its population with the Pfizer/BioNTech vaccine, so we may be able to gather enough data to answer this question more conclusively [30]. However, given what we know now, relying only on vaccination to reduce the transmission of the virus is not a sound strategy and the only proven method to reduce viral infection remains testing coupled with isolation/quarantine.

While increasing vaccination rates are cited as a significant factor for the declining number of COVID-19 cases [31], this explanation may be flawed as the transmission of respiratory illnesses is highly dependent on the number and nature of human contacts.

Rates of vaccination have significantly lagged the decline in the number of cases: the reported seven-day average in early January was ~250,000, which has fallen to ~70,000 by late February 2021. The number of reported cases has fallen to less than $\frac{1}{3}$ rd of its peak earlier this year but less than 10% of the population has been fully vaccinated; most vaccines are not fully effective until two weeks after the second inoculation. Given the time needed for vaccines to become effective, the gaps in this explanation become apparent.

A more likely explanation for the decline in the number of COVID-19 cases is that herd immunity for the variant, D614G, has reduced viral transmission. Unfortunately, if infection rates continue to trend upward (data from the last week in February), new variants may be successful at reinfecting previously infected individuals. Evidence from Brazil shows a strong likelihood that reinfection rates are rising quickly in the city of Manaus [32], a very troubling finding. We cannot conclusively distinguish between the effects of vaccination or the

possibility of herd immunity without more testing - we need to identify the cases that are now due to new variants.

Should the vaccines prove ineffective in reducing the spread of infection, public trust in vaccination may be further eroded. The vaccines' duration of efficacy and efficacy towards new variants also remains unknown. As an example of the fundamental problem, Roy Vagelos, former CEO of Merck, made the germane comment: "How do you compress a year's safety data into less time?" [33] Simply put, we cannot conclude that vaccination will be successful in ending the COVID-19 pandemic based on presently available data.

The logistical challenges of vaccination remain daunting, and as new variants proliferate requiring second-generation vaccines, risks of ADE (antibody-dependent enhancement) or VAH (vaccine hypersensitivity) also multiply. Recent work on SARS CoV-2 has not ended the debate on whether ADE is a continuing challenge for vaccine development [34] or whether VAH instead is the primary concern [35]. However, what is clear is that future vaccine development has become more complicated with potential interactions from both vaccines and the immune response from previous infections.

Second-generation vaccines have additional challenges beyond unknown risks. Adenovirus-based vaccines are unlikely to be easily modified since part of the immune system response is predicated on having a novel adenovirus delivery system. Thus, second-generation adenovirus vaccines require new vectors. Second-generation mRNA vaccines may have other issues, but at a minimum, scale-up and distribution remain difficult. There are now calls to develop a "pan-coronavirus vaccine" [36] - a daunting and seemingly impractical challenge: how do we develop a vaccine against a virus that does not yet exist?

4: Antiviral Drugs

There are now drugs with modest to significantly successful track records at reducing the progression of mild COVID-19 to severe disease. The use of Remdesivir, the first United States Food and Drug Administration (FDA)-approved treatment [37], is restricted to moderate to severe cases of hospitalized COVID-19 that do not require ventilation. U.S. clinical trials found that the drug's modest efficacy reduces the average length of hospital stays but

does not appear to reduce mortality [38]. However, an additional clinical trial showed promising results of a combination therapy of Remdesivir with the anti-inflammatory drug, Baricitinib [39] which both improved outcomes and reduced side effects. Conversely, the World Health Organization has concluded that Remdesivir alone is relatively ineffective [40].

Both the Regeneron REGN-CoV2 and Eli Lilly bamlanivimab antibody cocktails are being used under Emergency Use Authorization (EUA) rather than the usual approval process. The requirement that the antibody cocktails not be used on patients admitted to hospitals but only for outpatient care has meant that infusion care centers would be needed [41], leading to logistical challenges. Limited volumes and supply chain issues have also hindered access [42]; however, over ½ million doses were available as of Jan 05, 2021 [43]. It is probable that these drugs potentially reduced the number of hospitalized patients and prevented more severe diseases, although this remains speculative.

A New COVID-19 Strategy - Vaccination, Testing and Treatment:

Given these challenges, we must now identify a new path forward to defeat the COVID-19 pandemic. What are our options?

A more balanced approach to the COVID-19 pandemic would offer the potential to end the pandemic in the U.S. sooner and with less loss of life. To quickly defeat COVID-19, two technologies must be rapidly developed further: testing and antivirals. While extensive resources have been devoted to developing vaccines for COVID-19, both testing technologies and antiviral drugs have been given short shrift. There is no reason, other than economics, that vaccination or antiviral drug development must be an either/or situation and given the gravity and the high costs of the pandemic, pursuing all reasonable options is the most sensible strategy. New testing and antiviral drug technologies developed in the U.S. could also be exported to other countries, easing the global burden.

The Need for Improved POC Testing

There have been calls to rethink our testing strategy, as shown by a thought-provoking paper by Mina et al. [20]. POC options now include a CRISPR-based test, SHERLOCK [44], available under EUA. Other tests in development include antigen-based tests such as

RAPPID [45], while a saliva-based test that can yield results within seconds is also being commercialized. (www.blinkscience.com) It is beyond this paper's scope to go into testing technologies in more detail, but it is clear that several options are becoming available that make large-scale and rapid testing of the population feasible.

The Need for Better Antiviral Drugs

If we are to rely on testing to identify more infected individuals, then the need for better antiviral drugs becomes clear as vaccination will do nothing for a person with an active infection. Even Dr. Anthony Fauci, the chief proponent of vaccination, has acknowledged the need for COVID-19 antiviral drugs in a recent interview [46]. To date, antiviral drugs have had at best a modest impact on the COVID-19 pandemic. If we are to rely more heavily on antiviral drugs in a new COVID-19 strategy, we must understand why these drugs have not been successful.

Comparing Vaccines to Antiviral Drugs

The development of antiviral drugs for COVID-19 has been largely restricted to testing existing drugs repurposed from other infections rather than purpose-designed antivirals, in contrast to specific vaccine development.

As shown in Table 1, both vaccines and antiviral drugs have their uses. Most importantly, antiviral drugs can be employed to treat an existing infection, whereas vaccines can only be used prophylactically. Both technologies will benefit from increased testing but testing for antiviral drugs is critical to identify patients who might benefit. However, vaccination has been employed without testing even though prior infections may provide immunity against reinfection for at least eight months [47]. Whether this no-testing paradigm continues to hold with new variants and potentially second-generation vaccines remains to be seen.

Table 1: Comparison of Vaccine and Antiviral Technologies

Properties	Vaccines	Antiviral Drugs
Infection status	Will not treat an active infection	Treats active infections
Testing Requirements	Currently minimal, may change with new variants and vaccines	Requires identification of active infection
Potential Targets (of virus)	S, E, N, or M proteins only	Surface proteins plus >12 conserved proteins
Resistance Against New Variants	Limited	Can be high if the drug targets a conserved protein
Sterilizing Immunity	Possible, but not yet confirmed.	N/A
Number of Humans Treated	>200 million	Probably <20 million
Number of Medical Visits Needed	1-2	1
Safety	1 st generation very good, 2 nd generation unknown	Variable
Time for FDA Approval	>4 years typical	Can be <6 months
Side Effects	Currently limited	Unknown
Interaction Challenges	Significant	Limited
Residence Time in Body	~lifetime	Till cleared
Clinical Trial Size	Tens of thousands of patients	Hundreds to thousands of patients
Public Acceptance	Can be challenging	Straightforward

Source: Nanotech Plus, LLC (www.nanotechplus.net).

One of the major benefits of antiviral drugs compared to vaccines is the much broader array of targets. The review of Totura and Bavari noted several "druggable" targets among the conserved proteins of coronaviruses. Targeting conserved proteins removes the possibility of viral mutational escape and likely brings the pandemic to a close. The old jape of "a dead virus does not mutate" certainly applies. In contrast, vaccines are likely limited to targeting the S protein of SARS CoV-2 since patients with high levels of antibodies to the N protein fare poorly compared to patients with higher levels of S protein antibodies [48]. Thus, there are far more targets for antiviral drugs than vaccines.

In contrast to vaccination, the use of antivirals is much more straightforward and requires far fewer medical personnel. Vaccination can require 1 or 2 doses, each with monitoring medical personnel requirements, but typically, treating a patient with an antiviral drug requires a diagnosis and a prescription by primary care physicians. Since there should be far fewer interactions with medical personnel, rates of infection from obtaining treatment should drop.

Existing active COVID-19 infections are a small fraction of the total population and are likely < 5 million individuals at the end of February⁴. This means that only ~2% of the country needs to be treated at a given time- a much less daunting challenge than rapidly inoculating much of the country [49]. Furthermore, as patients are treated, overall infections should diminish. The calculation of how many people will need to be treated is beyond this paper's scope but is likely <20 million/year in the U.S.

What percentage of the population needs to be inoculated for herd immunity is not a straightforward question and depends on:

1. the percentage of the country that has already been infected,
2. reinfection rates of new and existing variants,

3. the efficacy of the vaccines against viral transmission of these new variants.

Clinical trials of current vaccines did not examine infection rates of pre-symptomatic/asymptomatic cases⁵ [50], and country-wide data is still needed to determine the effect of vaccination on the virus's transmission rates and its variants [51].

The COVID-19 vaccines developed so far have an excellent overall safety record to date - a remarkable achievement, while some antiviral drugs may have more severe side effects than vaccines. Balancing this risk is that antivirals are used on a much smaller segment of the population and for a shorter time. Antivirals are fully cleared from the body in a period of hours to months. Thus, clinical trials can quickly determine the efficacy and toxicity of antiviral drugs without abrogating existing safety and efficacy requirements. These clinical trials can be much smaller and faster than for vaccines. Unfortunately, overwhelmed hospital systems often no longer have the resources to gather data for clinical trials while caring for a daunting caseload. Even large pharmaceutical firms such as Pfizer are reporting challenges in gathering data for clinical trials of novel antiviral drugs [52].

Before the COVID-19 pandemic, establishing vaccine safety and efficacy generally took >5 years for an approved vaccine. While current COVID-19 vaccines have been safe and effective in the short term, their durability and efficacy for the longer term remain an open question. Calls for second-generation vaccines have disregarded the challenges of vaccine-vaccine interactions. Antiviral drug interactions will likely be far more modest.

Public acceptance of antiviral drugs is much more straightforward than vaccination, as few people refuse an antiviral drug if they have an infection. In contrast, vaccination for COVID-19 or other diseases remains a political hot potato.

⁴ A back of the envelope calculation here. There are ~60,000 reported infections/day as of Feb. 28 (7-day average), which likely means a total of ~ 400,000 infections (both reported and unreported) using the factor of 7 from the CDC. If infected individuals can spread virus for 10 days, then there are approximately 4 million active infections in the US as of Feb. 28, 2021, although this number may be falling currently. However, with the detection of new variants increasing, along with possible higher rates of reinfection, this current lull may be short lived

⁵ Vaccine efficacy was evaluated on the basis of reduction of severe disease as shown in the Pfizer/BioNTech vaccine here: www.fda.gov/media/144452/download

SARS CoV-2 Antivirals Under Development:

There is now a much larger effort underway to discover COVID-19 antivirals than at the beginning of the pandemic. The FDA's CTAP (Coronavirus Treatment Accelerated Program) lists close to 600 treatments under development, with over 400 programs in clinical trials and 300+ in late clinical trials [53]. Note that trackers such as the Milken Institute [54] often list a wide variety of therapeutics and antivirals, which makes an effort to discern novel coronavirus antivirals challenging. A large number of therapeutics under investigation is based upon the prevalence of the ACE-2 entry site in various organs ranging from the cardiovascular system to the brain and the gut.

Novel SARS CoV-2 Antiviral Technologies:

Several antiviral technologies are being developed for coronavirus antivirals ranging from antibodies to polymer drugs. (Some of these drugs were developed for other viruses.) Listed below are some representative examples of antiviral drugs that are either in or near to clinical trials.

Small Molecule Drugs

Pfizer PF-07304814

Pfizer has launched a Phase 1b clinical trial of a protease inhibitor (P.F.- 07304814) that was initially developed as a therapy for SARS CoV-1 [55]. This drug targets the 3CL protease (aka main protease or Main Pro), which is very similar in both SARS CoV-1 and SARS CoV-2. This protease is one of two cysteine proteases critical for viral replication since it produces several non-structural proteins used in viral replication and transcription [56]. Even though the compound is a prodrug with a phosphate group to increase solubility that gets cleaved, projected doses are quite high, in the 500 mg/day range, but synergistic activity with Remdesivir might lower the needed dose [57]. Unfortunately, it is proving difficult for Pfizer to recruit sufficient hospitalized patients for the clinical trials.

COVID Moonshot [58]

This group of 20 or so "Big Pharma" scientists/academicians are developing small molecule drugs to target the 3CL. It is a crowdsourced and crowdfunded effort that has

looked at over 16,000 structures and synthesized ~1,800 molecules [58, 59]. Unfortunately, the group is still attempting to raise \$1.5 million [60] to begin animal trials. With these funds, animal trials could hopefully be complete by summer 2021, enabling human clinical trials.

Merck's Molniravir

Merck's antiviral Molniravir (aka MK-48) was originally developed by Emory University and then licensed to Ridgeback Pharmaceuticals before being acquired by Merck. This drug's efficacy is based on a similar mechanism to Remdesivir. However, it is more soluble than Remdesivir, which may increase its efficacy. This pan-viral drug is a nucleoside analog that has previously shown some efficacy in influenza; however, nucleoside analogs often have toxicity issues. More recently, the drug has shown promising results in a ferret model [61], and the results of a Phase 2/3 clinical trial are expected early in 2021.

Atea 527

Atea Pharmaceuticals' AT-527 targets the RNA viral polymerase of SARS CoV-2. These enzymes have some conserved features in positive-sense RNA viruses, making them an attractive target for pan viral drugs [62].

Protein Drugs

Biologics are the fastest-growing pharmaceutical industry segment compared to small molecule drugs, and there are close to 400 protein drugs that have been approved [63]. Antibodies have been successfully used for some time to treat disease, although there have been few successful antibody antiviral drugs [64]. Like the new mRNA and adenovirus vaccines, new protein-based antiviral technologies may have their first successes against COVID-19.

Novartis/Molecular Partners

In October 2020, Novartis and Molecular Partners announced a partnership where Novartis would help commercialize two direct-acting antiviral drugs developed by Molecular Partners, MP-0420 and MP-0423 [65]. These compounds are small protein drugs that are designed to bind to multiple sites on the virus, which could help prevent mutational escape [66]. These drugs are not antibodies, so their production and scale-up in fermenters should be straightforward. Since these compounds are also more robust than antibodies, the need for a

cold chain may be obviated. Molecular Partners is currently conducting a Phase 1 clinical trial of the drugs, but Novartis will conduct the Phase 2 and Phase 3 trials if warranted.

Vir Biotechnologies

Vir Biotechnologies partnered with GSK and recently announced a Phase 1b/2a clinical trial soon for a new antibody-drug, Vir 7832 [67]. The clinical trials are part of the UK AGILE initiative [68]. The company claims that the antibody-drug may have the ability to clear the virus from the bloodstream and infected cells [69]. The antibody recognizes an epitope common to both SARS CoV-1 and SARS CoV-2.

Apeiron Biologics

Apeiron developed a drug, APN01, which mimics the ACE2 site. The theory is that this drug will "spoof" the virus into binding to the drug rather than the cell, reducing overall infection, as well as downregulating the *ras* system to reduce inflammation. The drug is currently

in Phase 2 clinical trials in Europe for hospitalized patients [70].

Polymer Drugs

Rather than use biologically based polymers, it is possible to design drugs using standard synthetic polymer chemistry. Nanoparticle drugs have shown that polymers can have a wide range of uses in pharmaceuticals and have been used to treat diseases ranging from hemophilia to hepatitis [71].

Nanoviricides

Nanoviricides has developed and scaled up its polymer platform technology. This novel approach involves decorating a polymer with a ligand that mimics the cellular target [72]. The company has been working on the technology for over a decade and rapidly pivoted to develop a SARS-CoV-2 drug from a prior SARS-CoV-1 compound.

Conclusions:

Our current strategy to defeat COVID-19 continues to rely heavily on vaccination rather than testing, isolation, and antiviral drugs. Given the high costs of this pandemic in both economic terms and human lives, it is critical to developing a layered defense. In case current vaccines do not prevent reinfection of the population by new variants, this greater depth of defenses certainly seems sensible. New testing and antiviral technology are available in practical terms but require political will to pay for development and deployment.

Acknowledgments:

The author would like to thank Charles Brumlik for his helpful discussion and to Jacqueline Fried who drew the artwork for this article. Funding for this paper has come from Nanotech Plus, LLC.

About the author:

Samuel Brauer, Ph.D., is the principal of Nanotech Plus, LLC, a consulting firm focused on commercializing advanced materials and founded in 2004. He received his doctorate in 1990 from Dartmouth College in bioinorganic chemistry and did postdoctoral work at UC Davis. He has helped commercialize antivirals for years and has given talks on nanomedicine (including vaccines) to groups such as the National Academy of Sciences, the Pharmaceutical Research Institute, and the Nanobusiness Commercialization Association.

Conflict of interest:

Dr. Brauer is a long-time shareholder in Nanoviricides, Inc. and has a modest financial position involving Moderna and Novavax. Mentioning companies constitutes neither the endorsement of products nor policies. For a signed statement, please contact the journal office editor@precision-nanomedicine.com

Refer to this article as: Brauer, S: Rethinking our COVID-19 Strategy, *Precis. Nanomed.* 2021;4(1):738-749. <https://doi.org/10.33218/001c.21569>

Bibliography:

1. Arkin D. U.S. reaches 500,000 deaths from the coronavirus. NBC News. 2021 Feb 22.
2. Belluz J. No ICU beds? Expect double the number of Covid-19 deaths. Vox Media. 2021 Jan 13.
3. Haseltine WA. Covid-19 Cases Are Rising Again Globally. Forbes Media. 2021 Feb 26.
4. Totura AL, Bavari S. Broad-spectrum coronavirus antiviral drug discovery. *Expert Opin Drug Discov*. 2019;14(4):397–412.
5. Wertheim JO, Chu DK, Peiris JS, Kosakovsky Pond SL, Poon LL. A case for the ancient origin of coronaviruses. *J Virol*. 2013;87(12):7039-7045.
6. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiamoorthy V, Abdool Karim Q, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021; 384(6):497-511
7. Sultana J, Crisafulli S, Gabbay F, Lynn E, Shakir S, Trifirò G. Challenges for Drug Repurposing in the COVID-19 Pandemic Era. *Front Pharmacol*. 2020;11:588654. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04321174) registration number: NCT04321174, NCT04342663, NCT04280705, NCT04244591, NCT04359329, NCT04348695, NCT04304313, NCT043505931
8. Herper M, Riglin E. Data show panic and disorganization dominate the study of Covid-19 drugs. *Stat News*. 2020 Jul 06.
9. Emanuel EJ, Cathy Zhang, Diana A. Where Is America's Groundbreaking Covid-19 Research? *The New York Times*. 2020 Sept 01.
10. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JC, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. *Elife*. 2020;9:e61312
11. Manzanares-Meza LD, Medina-Contreras O. SARS-CoV-2 and influenza: a comparative overview and treatment implications. *Bol Med Hosp Infant Mex*. 2020;77(5):262-273
12. Thomas L. Emergence of resistant SARS-CoV-2 variant in immunocompromised patient following therapeutic antibody use. *News Medical*. 2020 Dec 14.
13. The United States Centers for Disease Control and Prevention. c2021 [cited 2021 Jan 19] Available from: www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html
14. Reese H, Luliano AD, Patel NN, Garg S, Kim L, Silk BJ, et. al. Estimated Incidence of Coronavirus Disease 2019 (COVID-19) Illness and Hospitalization—United States. *Clinical Infectious Diseases*. 2020; ciaa1780
15. Johansson MA, Quandelacy TM, Kada S, et al. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. *JAMA Netw Open*. 2021;4(1):e2035057
16. The Covid Tracking Project. c2021 [cited 2021]. Available from <https://covidtracking.com/data/charts/us-all-key-metrics>
17. Service R.F. Fast, cheap tests could enable safer reopening. *Science*. 2020;369(6504):608-609.
18. Covid-19 tests are set to revolutionise the testing market. *Verdict Media Limited – Medical Device Network*. 2020 Dec 07.
19. Mina MJ, Parker R, Larremore DB. Rethinking Covid-19 Test Sensitivity - A Strategy for Containment. *N Engl J Med*. 2020;383(22):e120
20. Vandenberg O, Martiny D, Rochas O, van Belkum A, Kozlakidis Z. Considerations for diagnostic COVID-19 tests. *Nat Rev Microbiol*. 2021;19(3):171-183.
21. Plunging demand for COVID-19 tests may leave U.S. exposed. *Boston Globe*. 2021 Feb 27
22. National Institute of Allergy and Infectious Diseases (NIAID). cited2020 [cited 2020 Jan 09]. Available from: <https://www.niaid.nih.gov/diseases-conditions/ebola-vaccines>
23. Buchbinder SP, McElrath MJ, Dieffenbach C, Corey L. Use of adenovirus type-5 vectored vaccines: a cautionary tale. *Lancet*. 2020;396(10260):e68-e69.
24. Halstead SB. Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetra-valent dengue vaccine. *Hum Vaccin Immunother*. 2018;14(9):2158-2162.
25. Soucheray S. Fauci: Vaccine at least a year away, as COVID-19 death toll rises to 9 in Seattle. CIDRAP - Center for Infectious Disease Research and Policy – Office of the Vice President for Research, University of Minnesota. 2020 Mar 03.
26. The United States Centers for Disease Control and Prevention. C2021 [cited 2021 Jan 28] Available from: www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html

27. Haseltine W. New York Finds Its Own Covid Variants. The News Is Not Good. Forbes Media. 2021 Feb 26.
28. Callaway E. The coronavirus is mutating - does it matter? Nature. 2020;585(7824):174-177.
29. Cormier Z. The Second-Generation COVID Vaccines Are Coming. Scientific American, a division of Springer Nature America, Inc. 2021 Jan 20.
30. How Good Is the Israeli Pfizer Vaccine News? BloombergQuint. 2021 Feb 23.
31. Thebault R. Four reasons experts say coronavirus cases are dropping in the United States. The Washington Post. 2021 Feb 15.
32. Taylor L. Covid-19: Is Manaus the final nail in the coffin for natural herd immunity? BMJ. 2021;372:n394.
33. Vagelos R. 2020 Prix Galien Awards webinar. c2020 [cited 2020] Available from: www.galienfoundation.org
34. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. Nat Microbiol. 2020;5(10):1185-1191.
35. Halstead SB, Katzelnick L. COVID-19 Vaccines: Should We Fear ADE? J Infect Dis. 2020;222(12):1946-1950.
36. Stemmy E. Funding for Program Projects To Advance Pan-Coronavirus Vaccine Candidates. NIAID Funding News. 2020 Nov 18.
37. The Food and Drug Administration; c2020 [cited 2020 Oct 22] Available from <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19>
38. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-1826.
39. Paulsen SK. Remdesivir combo reduces COVID-19 recovery time. CIDRAP - Center for Infectious Disease Research and Policy – Office of the Vice President for Research, University of Minnesota. 2020 Dec 11.
40. Joseph A. WHO group recommends against using remdesivir to treat hospitalized Covid-19 patients. Stat News. 2020 Nov 19.
41. Lifespan Health System. Available from: <https://www.lifespan.org/centers-services/coronavirus-covid-19/covid-19-monoclonal-antibody-infusion-centers>
42. Rahhal N. Trump's covid 'cure' flop? States are only using 5-20% of their doses of coronavirus antibody treatments from Regeneron and Eli Lilly, Operation Warp Speed chief reveals. Daily Mail. 2020 Dec 15.
43. U.S. Department of Health and Human Services – Public Health Emergency. c2021 [cited 2021]. Available from: <http://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/allocation.aspx>
44. Sherlock Biosciences. c2021 [cited 2021]. Available from: <https://sherlock.bio/crispr-sars-cov-2/>
45. Ni Y, Rosier BJHM, Aalen E, Hanckmann E, Biewenga L, Pistikou A, et al. RAPPID: a platform of ratiometric bioluminescent sensors for homogeneous immunoassays. Biorxiv:363044 [Preprint]. 2020 [cited 2020 Nov 03]. Available from: <https://www.biorxiv.org/content/10.1101/2020.10.31.363044v1.full>
46. American Medical Association. [Internet]. c2021 [cited 2021 Feb 03]. Available from: <https://edhub.ama-assn.org/jn-learning/video-player/18582580>
47. Cassata C, Cassell DK. How Long Does Immunity Last After COVID-19? What We Know. Healthline. 2021 Feb 24.
48. Batra M, Tian R, Zhang C, Clarence E, Sacher CS, Miranda JN, et al. Role of IgG against N-protein of SARS-CoV2 in COVID19 clinical outcomes. Sci Rep. 2021;11(1):3455.
49. Mayo Clinic [Internet]. c2021 [Cited 2021]. Available from: <https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/herd-immunity-and-coronavirus/art-20486808>
50. The Food and Drug Administration; c2020 [cited 2020 Dec 17] Available from www.fda.gov/media/144452/download
51. Mallapaty S. Are COVID vaccination programs working? Scientists seek first clues. Nature News. 2021 Jan 22.
52. Griffin R. Pfizer Struggled to Recruit for Covid Drug Trial as Cases Soared. Bloomberg. 2021 Jan 08.
53. The Food and Drug Administration. Available from: <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>

54. Milken Institute Covid-19 treatment and vaccine tracker. c2021 [2021 Mar 14]. Available from: https://covid-19tracker.milkeninstitute.org/#treatment_antibodies
55. Pfizer [Internet]. c2021 [2021 Jan 25]. Available from: <https://www.pfizer.com/science/find-a-trial/nct04535167>
56. Boras B, Jones RM, Anson BJ, Arenson D, Aschenbrenner L, Bakowski MA, et al. Discovery of a Novel Inhibitor of Coronavirus 3CL Protease as a Clinical Candidate for the Potential Treatment of COVID-19. Biorxiv:293498 [Preprint]. 2020 [cited 2020 Sept 13]. Available from: <https://www.biorxiv.org/content/10.1101/2020.09.12.293498v2>
57. Halford B. Pfizer's novel COVID-19 antiviral heads to clinical trials. c&en News. 2020 Sept 17.
58. COVID Moonshot-Postera. [Internet]. c2020. Available from: <https://covid.postera.ai/covid>
59. Delft F.V. COVID Moonshot Webinar -- 2020 Progress and 2021 Outlook. c2020 [cited 2020] Available from: <https://www.youtube.com/watch?v=fkQwDltGDfU>
60. Scudellari M. COVID Moonshot Effort Generates "Elite" Antivirals. IEEE Spectrum. 2020 Dec 04.
61. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analog MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat Microbiol. 2021;6(1):11-18.
62. Buonaguro L, Tagliamonte M, Tornesello ML, Buonaguro FM. SARS-CoV-2 RNA polymerase as target for antiviral therapy. J Transl Med. 2020;18(1):185.
63. Usmani SS, Bedi G, Samuel JS, Singh S, Kalra S, Kumar P, et al. THPdb: Database of FDA-approved peptide and protein therapeutics. PLoS One. 2017;12(7):e0181748.
64. Ahangarzadeh S, Payandeh Z, Arezumand R, Shahzamani K, Yarian F, Alibakhshi A. An update on antiviral antibody-based biopharmaceuticals. Int Immunopharmacol. 2020;86:106760.
65. McGrail S. Novartis to Develop Direct-Acting COVID-19 Antiviral Therapies. Pharmanews Intelligence. 2020 Nov 06.
66. Novartis and Molecular Partners – MP0420 and MP0423. Genetic Engineering & Biotechnology News. 2020 Nov 09.
67. GSK and Vir Biotechnology to initiate NHS-backed Covid-19 trial. Clinical Trials Arena. 2021 Jan 14.
68. Agile Clinical Trial Platform. [Internet] Available from www.agiletrial.net
69. Vir Biotechnology, Inc. [Internet] c2021 [cited 2021 Jan 26]. Available from: <https://investors.vir.bio/node/7756/html#d54514dex991.htm>
70. APEIRON Biologics: Patient recruitment completed in Phase II COVID-19 Clinical Trial of APN01. Pharmaweb.com Limited. 2020 Dec 04.
71. Ventola CL. Progress in Nanomedicine: Approved and Investigational Nanodrugs. P T. 2017;42(12):742-755.
72. Prof. Francesco Stellacci of EPFL has been exploring a similar approach. See:
73. Prof. Francesco Stellacci. Swiss Federal Institute of Technology Lausanne (École polytechnique fédérale de Lausanne - EPFL). Available from: <https://people.epfl.ch/francesco.stellacci?lang=en>