

A proposal for long-term COVID-19 control

Universal vaccination, prophylactic drugs, rigorous mitigation, and international cooperation

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GLOBAL WORKING PAPER #160
AUGUST 2021

B | Global Economy
and Development
at BROOKINGS

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August 2021

Brookings Global Working Paper #160

Global Economy and Development program at Brookings

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Acknowledgements

William A. Haseltine is Chairman and President, ACCESS Health International, Inc. Mr. Haseltine is a Trustee of the Brookings Institution, and provides financial support for Brookings. Brookings is committed to quality, independence, and impact in all of its work.

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Introduction

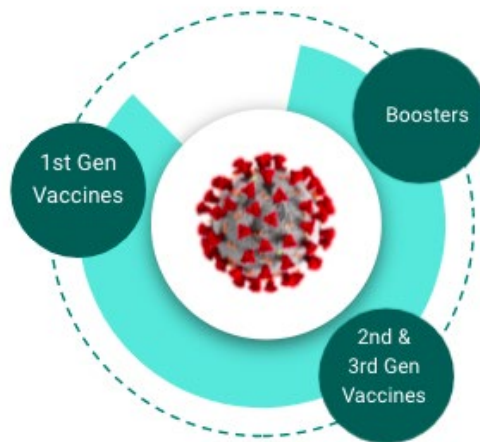
Four successive waves of COVID-19 have buffeted the United States for the past year and a half. With each wave, we have bet on different measures to push us through: First, public health measures, then drugs and treatments, and now, with our fifth wave, we hold out hope for vaccine-led recovery. But from the outset, we have underestimated this virus and its ability to maneuver the public health battleground; it is escaping the best defenses we are able to muster and finding new avenues of attack.

In this paper, I propose a multimodal strategy for long-term COVID control, one that sets up multiple barriers of protection so that we are able to not only contain SARS-CoV-2 and eliminate COVID-19 as a major life-threatening disease, but also return to a new social and economic life. The strategy uses the best of what we have on hand today—a rapidly growing arsenal of vaccines and antiviral drugs and public health measures—with an eye towards future improvements and developments.

The most immediate priority should be supporting additional research on the molecular biology of SARS-CoV-2, of which we still know surprisingly little. This is particularly important since there is great likelihood that COVID-19 will [become endemic](#).¹ Unlike the viruses that cause smallpox or polio, SARS-CoV-2 has demonstrated an impressive ability to adapt and thrive in both humans and animals, including our much-loved pet, cats and dogs. Even if we can eliminate the disease from our own communities, it is unlikely we can do the same across the globe and for all our animal populations at the same time.

The best we can hope for is containment of COVID-19 at levels we can tolerate both personally and economically. We have to use all the tools we have at our disposal—being aware of the inequities and disparities from country to country and within countries—that have made this and other diseases so hard to address.

Vaccines



Vaccines, today, are the “*sine qua non*” or necessary reality of COVID containment. Without vaccines, most efforts will be temporary at best. Fortunately, we have vaccines that are effective and safe. The current generation of vaccines, especially the mRNA vaccines produced by Pfizer/BioNTech and Moderna, are effective against the original wild-type virus and many of its known variants. Clinical trials showed these mRNA vaccines were initially [around 95 percent effective](#) at preventing infection and severe disease.² As new variants have emerged—Alpha, Beta, Delta, and Gamma—effectiveness of each vaccine has varied, though current estimates suggest they are [at least](#) 64 percent effective against infection and may be even more effective against severe disease at least shortly after vaccination.^{3,4,5} Other vaccines, like the AstraZeneca, Johnson & Johnson, and Sinovac, are more moderately effective against the original wild type and fare more poorly against the variants.^{6,7}

Effective vaccines that are known to prevent symptomatic infection and severe disease are critical to controlling the spread of the virus. But as the virus evolves, so too does our understanding of whether vaccines alone will ever be sufficient to stop the virus. From what we know today, vaccines alone will not be enough.

First, vaccines don’t work for everybody. Even in the best-case scenarios, against the original wild type virus, they still fail 5 percent of the time. To put that in perspective, even if every American was vaccinated, 17.5 million people would still be at risk of infection and disease if exposed to the virus.

Adding to that, there are also substantial populations of people with underlying conditions that render them at least partially resistant to the positive effects of

vaccination, these include [organ transplant recipients](#), people taking certain [immune suppressing drugs](#), those undergoing cancer therapy, people with inherited genetic disorders, as well as a fraction of the [elderly population](#) who has developed antibodies to interferon or have other age-related immunity issues.^{8,9,10}

While vaccines may be highly effective at preventing disease, they are not equally effective at thwarting infection. From what we know today, the Delta variant has already become somewhat adept at working its way past our vaccine protections. Indeed, recent studies have shown that those who are vaccinated but still become infected can carry the [same amount](#) of virus in their systems as those who are unvaccinated and infected.¹¹ This means that while vaccines may protect those who are vaccinated from severe illness, they may not protect those around them from infection. We had warnings of this prior to the studies themselves being released. The latest outbreak in Singapore, which caused the nation to lock down again for more than a month, originated from [vaccinated airport workers](#) who were infected by travelers, who then passed it onto others in the community.¹² Worse yet, in May and June 2021 new cases peaked to all-time highs in Chile despite having one of the best vaccination rates in the world: 82 percent of the population were vaccinated with one dose of Sinovac/Coronovac and 70 percent received two full doses at the time of the upsurge.

Like protection offered by the influenza vaccine, early evidence suggests that COVID vaccine-induced immunity may fade over time. [Early data](#) showed the Pfizer-BioNTech vaccine offers 95 percent protection against infection shortly after the second dose, but that protection faded to 70 percent efficacy after 200 days and 50 percent efficacy at 250 days.¹³ Those numbers may fall more rapidly in the face of new variants.

Booster shots have been pegged as a possible solution to the problem of fading immunity. Some manufacturers have already started [clinical trials](#) to test the effectiveness of boosters and whether they are more effective if they are tailored to respond to dominant variants circulating in a region. Tailored vaccines are also being developed, using the same methods as those in distribution today, to create a stronger immune reaction to specific variants circulating.

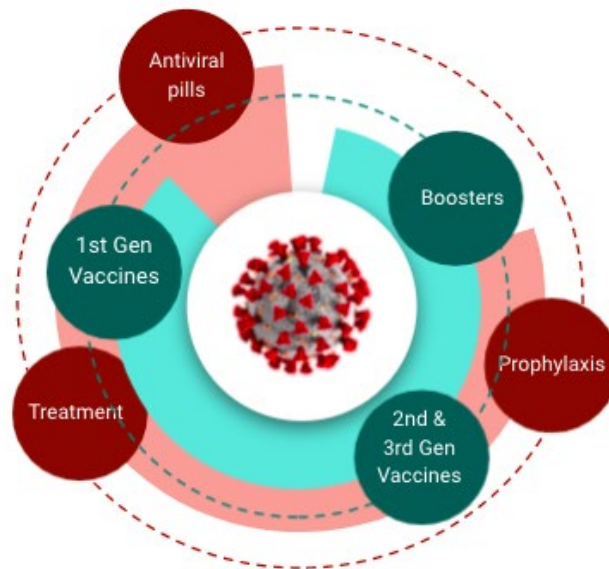
However, one issue with creating variant-specific vaccines is that the variants seem to be able to outpace our fastest vaccine manufacturing and distribution capabilities; by the time tailored vaccines and booster shots make it into the arms of those in need, it may already be too late to stem an outbreak. Another issue is that the more vaccine-acquired immunity circulating in a community, the more opportunities the virus has to adapt and learn new ways to evade our immunity. As a [study](#) from the Scientific Advisory Group for Emergencies in the U.K. puts it, vaccines that prevent severe disease are critical to our efforts today, but a longer-term solution requires vaccines

that also induce high and durable levels of mucosal immunity to reduce infection of and transmission from vaccinated individuals.¹⁴

In addition to those specific vaccine efforts, there are also two other types of third generation vaccines that may provide more promising solutions. The first type are vaccines that may allow for easier manufacturing and distribution of doses, such as single dose vaccines, noninjectable vaccines, or double dose vaccines that do not require cold chain storage. The second type are vaccines that could protect against all SARS-CoV-2 variants and possibly even other coronaviruses—mosaic vaccines that present multiple antigens in one dose and may lead to protection against a broad array of variants.^{15,16}

Still, no matter how good our vaccines become, we will always face issues with deploying them worldwide in a timely manner. While these challenges are solvable over time, a single truth remains for now: vaccines alone will not end the pandemic.

Antiviral treatment and prophylaxis

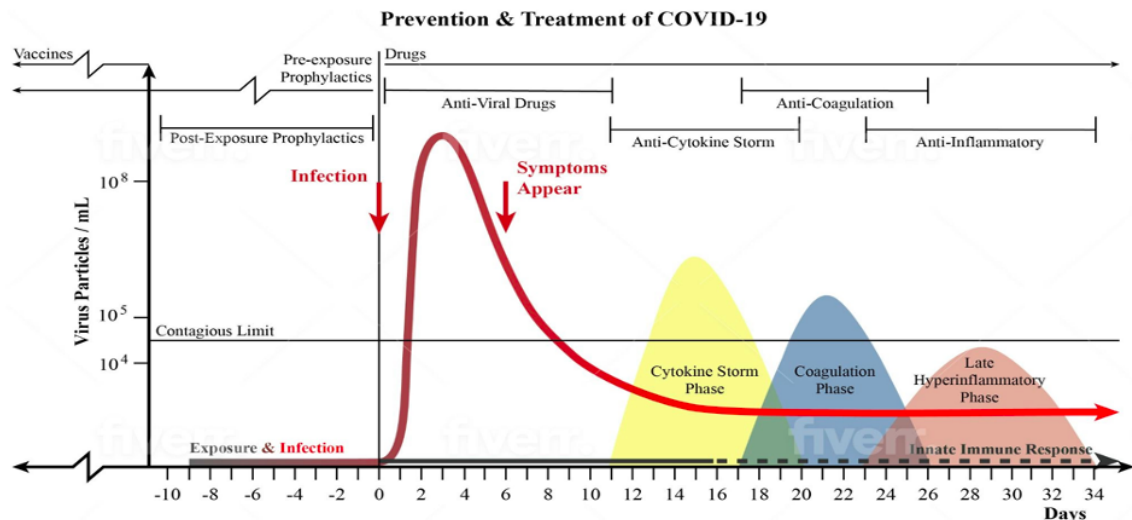


To fill the gaps in vaccine protection, we can create a second ring of defense with antiviral drugs. The US government recently committed \$3.2 billion to develop antiviral pills for COVID-19. While much of the talk is around the use of these drugs as a treatment for COVID-19, their real power is in their prophylactic use: preventing people exposed to the virus from ever becoming ill or passing on an infection.

As a treatment, these drugs could have a profound effect for immunocompromised patients with chronic viremia—or, simply put—those with high levels of the virus in their bodies over an extended period of time. [Studies](#) have shown that even after months of living with the virus, antiviral treatments can clear the viremia and eliminate symptoms of the disease, hopefully to never return.¹⁷ The challenge today is that the virus is learning to adapt and [develop resistance](#) to the antivirals currently in use, which means we need to develop combinations of drugs in the future to prevent the virus from resisting the antiviral effects.¹⁸

Antivirals could also be an effective treatment for the average person infected by SARS-CoV-2. If administered early enough in the course of the disease, antivirals can prevent the disease from progressing. The use of antiviral cocktails has already been approved for use prophylactically.¹⁹ But the problem is in the timing. By the time symptoms of COVID-19 appear, it may already be too late for antivirals to help stop the spread of the virus in the body. This means that if people are not testing themselves regularly, they may not know they are infected in time to take the drugs.²⁰

The third and perhaps most important potential use for antivirals is as a prophylactic—taken by those exposed to the virus to prevent them from becoming infected. The problem with this approach today is that the current generation of drugs are expensive to produce and cumbersome to administer, requiring an intravenous infusion in a clinical setting. Because of this, they cannot yet be used widely as a prophylactic. However, there is a [proof of principle](#) to show the potential benefits of the approach.²¹



The next generation of antivirals will ideally come in pill form. Imagine the potential of such a drug in, for example, a long-term care setting where one resident tests positive for COVID-19 and other residents are high risk organ transplant or immunosuppressed individuals who cannot rely on the protections from vaccines. With antiviral

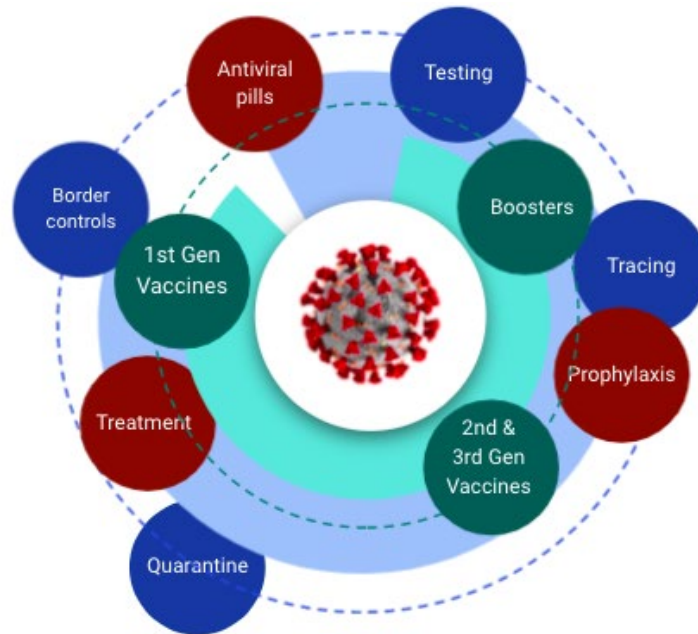
prophylactic pills, these residents could be protected from infection with the help of a simple pill—allowing them and the infected patient to continue sharing the same communal living space. The same approach applies to schools, businesses, professional sports teams, even ships at sea; if one among the many tests positive for COVID-19, those around him/her could take a pill to help stave off a potential infection.

The \$3.2 billion funding commitment is an important step to developing new antivirals that will be cheaper to produce, easier to take, and more effective at preventing the virus from immunological escape. Cocktails of antiviral drugs can work on multiple targets at the same time and make it harder for the virus to develop resistance. If available as pills, the drugs will be easy for anyone to take prophylactically once they know they have been exposed, as easy as Xofluza (baloxavir) that people take today to prevent the flu or Tamiflu (oseltamivir), its less effective cousin. And similar to vaccines, there is the possibility of a longer-term solution farther down the line—slow release, [long-acting antivirals](#) that may offer a person protection from infection for six months up to a year.²²

The advent of prophylactic drugs in pill form will also have an enormous impact on public health containment efforts as described in the section below. As opposed to testing, tracing, and quarantining to avoid spreading further infection, the mantra may become test, trace, and prophylactically prevent—a much more attractive alternative to isolating alone in a room at home. While some [barriers](#) to contact tracing, like concerns around privacy, may always remain, it is possible that other barriers will fall when the threat of quarantine disappears and people no longer worry about losing their livelihoods or income by quarantining for two weeks in the face of exposure.²³ Antiviral prophylaxis may also help reopen borders and reignite global travel, as drugs could be taken prior to and during travel, limiting the need for extended quarantines for travelers upon arrival in a new country or region.

As SARS-CoV-2 variants continue to burst through our best vaccine defenses, prophylactic drugs can help shield us. Vaccines and antivirals work in different ways, and resistance or escape from one does not mean the virus can break away from both defenses when used in tandem. Indeed, the combined use of vaccines and prophylaxis may be the closest thing to a surefire strategy.

Public health containment



Countries like Australia, China, New Zealand, Singapore, and Taiwan used individual public health behaviors, like mask wearing and social distancing, along with more organized efforts around testing, contact tracing, isolation, and quarantine to nearly eliminate the virus in their countries. These tried and true strategies have been critical methods of protection in the face of nearly every infectious disease in recent history, and are enhanced by the drugs and vaccines we have for COVID that can help reduce the burden of quarantine, ease the scope of new outbreaks, and as found in a recent modeling study, improve our ability to contain and control vaccine-resistant strains.²⁴

Yet, despite the effectiveness of these measures, viruses like SARS-CoV-2 can still find ways to pierce this ring of defense. Known and emerging COVID variants have mutated to ever-increasing levels of transmissibility to overcome even the strictest adherence to these public health standards. In Australia, for example, a Melbourne man was quarantined in a monitored facility on the same floor as another traveler who eventually tested positive for the highly infectious Kappa variant. Though the two individuals had no direct contact with each other, they opened the doors to their quarantine hotel rooms within [30 minutes](#) of each other, starting an outbreak, which went on to expose more than 17,000 people to the virus and which could only be contained with another round of lockdowns.²⁵

In Guangzhou, China, the fifth largest port city in the world, another highly infectious variant, the Delta variant, swept through the city in under two weeks, despite the high volume testing and contact tracing that the city had been conducting throughout that time. And in Singapore, despite vaccinations, the Delta variant has spread from the airport to and throughout the local community. This reinforces the idea that public health containment is an important strategy to contain the virus but one that cannot be used alone in the long-term.

Here in the United States, we have yet to ramp up our public health protection measures to adequate levels. Indeed, the few measures that were in place, such as mask wearing and social distancing requirements in places of work, worship, study, and gatherings, are quickly being dropped. Our COVID testing programs have also not yet gotten off the ground more than a year and a half into the pandemic. We need to ramp up the availability of rapid tests at all schools, businesses, and public events, as opposed to trusting that Americans will test themselves before entering a crowded indoor area. Making home tests more readily available at an affordable price would also be a critical next step.

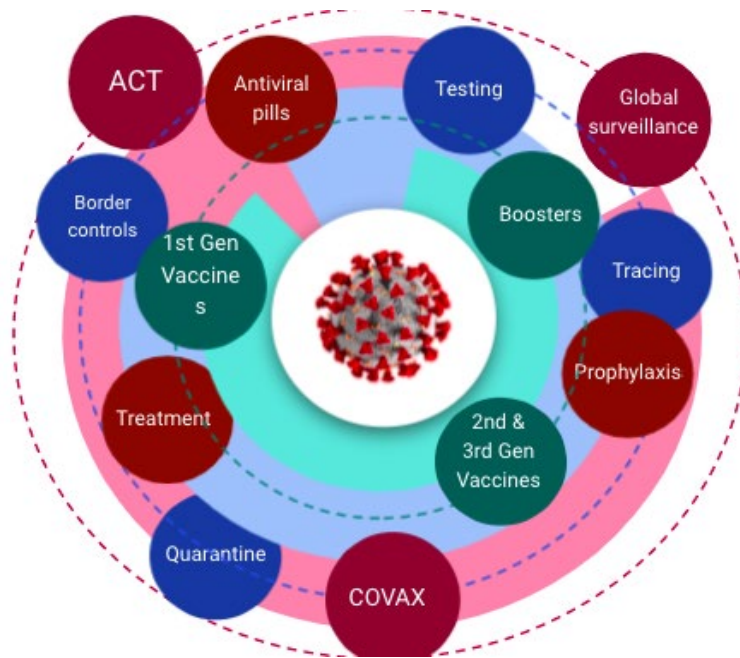
Beyond testing, there is a need to ensure we have a fully mobilized and operational contact tracing program to identify all those who come into contact with someone who tests positive and encourage them to quarantine to avoid spreading the disease. The current administration has already committed to building an army of 100,000 contact tracers, but a recent survey by NPR and Johns Hopkins Center for Health Security found that more than half of the 36 state health departments included in the survey were actually winding down their contact tracing programs, with fewer tracers in May 2021 than they had in December 2020.²⁶ The vast majority said they had no intention of hiring more contact tracers in the future.

At the same time, we should be ramping up other surveillance efforts that can identify community outbreaks and contain their spread like the Centers for Disease Control's (CDC) new National Wastewater Surveillance System. If we can identify an outbreak in a community early enough, we can give people in those communities priority access to vaccines and antiviral pills when they become available and help those who are unprotected by any other means to isolate safely and in a supported environment with access to food, income, and other resources necessary for their well-being.

But identifying those who may have been exposed does not guarantee that those people will quarantine for two weeks. In many cases, many people fear losing their jobs and steady income by missing work, not an insignificant obstacle to overcome. One way to address this issue is if the U.S. government was prepared to support assisted isolation, folding in a cash incentive to replace lost income and encouraging participation among those who might otherwise be hesitant to report that someone in

the household was infected. Already states are offering monetary incentives, up to \$100, to encourage people to protect themselves and others around them through vaccination. Extending these incentives to include other COVID-19 control measures like quarantining could significantly improve adherence rates. Granted, the costs would be high—depending on the size of the epidemic, costs could be well into the tens of billions of dollars but that is still arguably less than the trillions at stake as our economy struggles with an extended outbreak or regular waves of infections and deaths in the years to come.

Global containment



The first three layers of protection are, together, an excellent defense. But they will work best when the global community works together to further SARS-CoV-2 research, identify new medical solutions, collaborate on global disease surveillance, and ensure universal access to tests, treatments, and vaccines.

The Access to COVID-19 Tools (ACT) Accelerator and its vaccines pillar, COVAX, is an important first step. ACT is a global philanthropic partnership to accelerate the development and production of COVID-19 tests, treatments, and vaccines (via COVAX) and, perhaps most critically, on ensuring that all people and countries can access and afford these measures. So far, COVAX has helped deliver more than 175 million vaccine

doses to 138 countries. But to date it has only raised about half of the money it needs to provide protection for the world.

In addition to ramping up efforts to fulfil ACT's goal, the global community will also need to intensify the effort to help identify new outbreaks, especially ones caused by highly infectious and transmissible variants. This means all countries must enhance surveillance efforts, increase sequencing of the virus across all communities, and develop a near real-time method of sharing the data broadly. Then the onus falls on the global community of scientists, researchers, and vaccine and drug manufacturers to quickly determine how vaccines and treatments fare against each new variant and what can be done to mitigate their spread and reduce the emergence of new variants.

To do that, we need to significantly expand our understanding of SARS-CoV-2 and its molecular biology. We now know that we do not yet know enough about the virus and how it works. Without this knowledge, we cannot develop the tools to defeat it. This is the main argument behind a substantial influx of global funding for fundamental research on SARS-CoV-2 and coronaviruses more broadly. No single lab or single scientist can develop this knowledge quickly enough on their own, but we have seen throughout this pandemic how quickly a global community of scientists, fully resourced and compelled to work collaboratively and transparently, can unearth new findings.

The battle between man and virus is shaping the course of human history and will continue to impact our lives. This virus has already transformed life as we know it for this generation and the next. A year and a half into this pandemic, we have what we need to end the pandemic but we must be willing to apply what we know. This comprehensive, multimodal strategy is a surefire way to end this pandemic and rebuild a world that is prepared to take on future COVID outbreaks and other diseases as yet unknown.

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