



HIT HARD HIT FAST HIT GLOBALLY

A MODEL FOR
GLOBAL VACCINE ACCESS

ACKNOWLEDGMENTS

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ABOUT PREP4ALL

PrEP4All is a national nonprofit organization committed to ensuring that the most vulnerable individuals can access HIV prevention and treatment regardless of race, gender, socioeconomic status, or geographic location. Founded by patients in 2018, we work with community members and public health experts to pressure government officials to ensure everyone can get the HIV care they need. In 2020, we began working on COVID-19 drug access, and have since advocated for increased access to COVID-19 drugs and vaccines.

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EXECUTIVE SUMMARY

The development of highly effective COVID-19 vaccines represents a milestone in the response to the pandemic. However, without global access to these technologies, they cannot achieve their full potential to save lives and spur economic recovery worldwide.

Without a goal of global epidemic control, vaccine resistant variants will arise, undermining the domestic vaccination campaign, increasing further spread of COVID-19, and costing the U.S. government hundreds of billions of dollars.

The United States has a unique opportunity to avert this crisis by scaling up production of the most effective vaccine candidates and ensure quicker and more comprehensive immunization, paving the way for global epidemic control.

This report serves as a blueprint for a public-private partnership to manufacture enough mRNA vaccines to vaccinate the world, all with a capital investment of an estimated \$4 billion. It includes a discussion of why global immunization is necessary, a comparative look at the various vaccine technologies, a plan for building vaccine manufacturing capacity in the United States and the world, and an analysis of the public health and economic impact this plan would have.

Viruses know no borders, so the development of viral variants in other countries poses not only a threat to lives abroad, but also to American lives.

American biosecurity relies on an effective global vaccination strategy, which must be built on the following core tenets:

HIT HARD

The production and development of highly effective vaccines must be prioritized to reduce the risk of vaccine resistant variants and more rapidly achieve herd immunity.

HIT FAST

By inoculating a large portion of the population rapidly with highly efficacious vaccines, herd immunity can be achieved sooner, saving lives, allowing the process of economic recovery to begin, and reducing the opportunity for development of vaccine resistant variants.

HIT GLOBALLY

Global vaccination further protects against vaccine resistant variants arising in other countries and subsequently spreading to the United States, undermining immunization efforts domestically.

Unfortunately, the current approach to global vaccination does not achieve any of these goals. Current plans for global vaccination focus on less effective vaccine candidates — some of which are already ineffective against

emerging variants. Furthermore, even the most optimistic estimates project that global vaccination will not be achieved until 2023 without a new strategy. Such a paradigm ensures the development of vaccine resistant variants that could cause a resurgence of COVID-19 in the United States — even after herd immunity is achieved here. Finally, disparities in vaccine access between rich and poor countries not only threaten global public health, but also geopolitical stability and the global economy. Indeed, a recent study from the International Chamber of Commerce found that current vaccine disparities would deprive the world economy of up to \$9.2 trillion, costing the United States up to \$1.3 trillion.

Private vaccine manufacturers are unlikely to remedy current vaccine shortages. In non-pandemic times, demand for vaccines is relatively low — approximately 3.5 billion doses per year for all vaccines combined. Once the COVID-19 pandemic is contained, demand will likely return to these levels, and enough manufacturing capacity to vaccinate the entire world annually will not be required. Private vaccine manufacturers are thus disincentivized from investing in building adequate vaccine manufacturing capacity to meet current global need. This represents a classic “market failure” — in which market forces, absent government intervention, do not result in an optimal allocation of resources. In this case, private vaccine manufacturers are not properly incentivized to increase production capacity to meet global demand, especially when most of this unmet demand is for low- and middle-income countries (LMICs) that are likely unable to pay a premium price for each dose.

The U.S. government can alleviate this failure by increasing global mRNA production capacity and ensure global immunization by the beginning of 2022. In doing so, the United States would reestablish global public health leadership, stimulate economic recovery, and save millions of lives.

For less than the U.S. government spends on the COVID-19 response daily, it can build a facility to produce enough mRNA vaccine manufacturing capacity to vaccinate the entire world in one year, with each dose costing only \$2. By contracting the operation of the facility to a private company, production can be rapidly scaled-up using existing know-how. Crucially, this facility would be owned by the U.S. government, providing the United States with mRNA vaccine manufacturing capacity to produce

boosters against new variants and vaccines for future pandemics. The Department of Energy already uses this model for its national laboratories. Repurposing this model for public health ensures that the federal government address the current crisis while preparing for the next pandemic.

mRNA vaccines are particularly attractive for scale-up. Their nearly cell-free production process makes them easier to produce and scale than other technologies, making them more suited for adaptation to combat new variants. In the past year alone, commercial production for mRNA vaccines has grown from zero to over 3 billion doses per year. The vaccine developed via collaboration between the National Institutes of Allergy and Infectious Disease (NIAID) and Moderna can also be stored at normal freezer (0°F) and refrigerator (40°F) temperatures, making it easier to distribute than the Pfizer/BioNTech mRNA vaccine, which requires deep freezing (-90°F) for storage beyond two weeks. Finally, the NIAID/Moderna vaccine was funded almost exclusively by the U.S. government (\$2.5 billion invested so far) and relies heavily on intellectual property invented and owned by the United States. Thus, the United States has unique leverage with Moderna. Working closely with Moderna, the U.S. government should scale up this vaccine technology as rapidly as possible.

mRNA vaccines can be scaled up rapidly with relatively small capital costs. An investment of approximately \$4 billion from the United States would build enough capacity to manufacture 16 billion doses per year — enough to vaccinate the entire global population. Federal laws like the Defense Production Act and 28 U.S.C. §1498 could accelerate this process by prioritizing and sourcing vaccine feedstock components, protecting smaller suppliers from patent infringement liability while rewarding innovators.

The previous administration’s decision to abandon America’s traditional role in global public health has left a leadership vacuum that will fuel social unrest around the world. Already, vaccine shortages are threatening stability, costing the global economy billions of dollars, and jeopardizing the health of millions, including American citizens. The Biden Administration can fill that vacuum, strengthening diplomatic relations with other nations while simultaneously protecting American citizens from emerging variants and strengthening the U.S. economy. By building publicly-owned vaccine manufacturing capacity, the United States can solve the current pandemic and build the infrastructure needed to support biosecurity for decades to come.



INTRODUCTION

“

I simply wish that, in a matter which so closely concerns the well-being of mankind, no decision shall be made without all the knowledge which a little analysis and calculation can provide.

”

— D. BERNOULLI (1700-1782), ON SMALLPOX INOCULATIONS

The rapid development of highly effective and safe COVID-19 vaccines represents a milestone in the response to the pandemic.

Two mRNA vaccines — one developed by a collaboration between the U.S. National Institute of Allergy and Infectious Disease (NIAID) and Moderna Inc. (Moderna) and another developed by a collaboration between Pfizer Inc. and BioNTech SE — have demonstrated over 90% efficacy in preventing symptomatic SARS-CoV2 infection in phase 3 randomized control trials.^{1,2} Multiple other vaccine candidates have also proven safe and effective to varying degrees and are also in use. Yet, current vaccine shortages threaten to undermine the public health potential of these technologies, and ultimately, our ability to bring the COVID-19 pandemic under control.

The World Health Organization³ (WHO) and the U.S. Food and Drug Administration⁴ (FDA) initially established relatively low efficacy standards for COVID-19 vaccines — only needing to show a 50% reduction in symptomatic disease compared to placebo. These guidelines reflected the reasonable assumption that the first vaccines may not be extremely efficacious, and thus, would be used as a form of **epidemic mitigation** (i.e. reducing the mortality and morbidity of COVID-19) — like a seasonal influenza vaccine — rather than **epidemic control and elimination** (i.e. eliminating widespread community transmission of SARS-CoV-2, the virus that causes COVID-19). The advent of highly effective COVID-19 vaccines, like mRNA vaccines, however, means the world can, and must, aim to achieve epidemic **elimination** for

SARS-CoV-2 transmission. While using less effective vaccines — and triaging limited doses to those who are most vulnerable, rather than universal vaccination — is better than no vaccination at all, this sub-optimal option allows for continued widespread community transmission, posing a significant risk for individuals who are not vaccinated. The failure of the WHO to publicly aim to achieve epidemic elimination for SARS-CoV2⁵ — or even state that it is a goal of current global public health efforts — represents a dangerously unambitious approach to responding to the COVID-19 pandemic.

Continued widespread transmission of SARS-CoV-2 also allows the virus an opportunity to evolve resistance to both naturally acquired and vaccine-induced immunity — a phenomenon commonly called “antigenic drift”.⁶ Antigenic drift will be a significant challenge for any approach to epidemic control and elimination. Even before the current COVID-19 pandemic, antigenic drift has posed a challenge for our ability to stem the spread of other coronaviruses. For example, antigenic drift in seasonal coronaviruses that cause common colds may be responsible for reinfecting individuals who have already recovered from, and developed immunity to, previous infections with the same coronaviruses.⁷ Variants of SARS-CoV-2 have already emerged that appear to significantly increase the transmissibility of the virus⁸ and dramatically reduce the ability of some vaccines to prevent symptomatic COVID-19.⁹

mRNA vaccines are uniquely suited for combatting COVID-19. Not only are they extremely effective and easy to produce, but they can also be adapted far

more rapidly to combat new viral variants that evolve resistance to existing vaccines. Currently, the bulk of planned global vaccine production relies on less effective vaccine candidates, like the one developed by a collaboration between AstraZeneca and the University of Oxford, that are unlikely to be able to achieve epidemic control and elimination even if one hundred percent of a population is vaccinated. Even worse, the world's current multilateral facility for vaccine procurement for low- and middle-income countries (LMICs), COVAX, only aims to vaccinate 27% of these countries' populations by the end of 2021.¹⁰ Not only will this result in potentially millions of unnecessary deaths, hospitalizations, and longstanding and possibly permanent challenges to physical and mental well-being related to infection with SARS-CoV2, but also all but guarantee generation of vaccine-resistant variants.

Critically and less understood, vaccine access is not just a question of public health, but also global stability. Indeed, a senior European Union official warned that lack of vaccine access in LMICs could "develop into a question of war and peace."¹¹ The consequences of the economic downturns related to COVID-19 mitigation measures are a key factor. A recent study from the International Chamber of Commerce found that current global vaccine shortages would deprive the world economy of up to \$9.2 trillion, with the United States shouldering a disproportionate brunt of that cost.¹² Without bold leadership, efforts to control the further spread of COVID-19 will fail, perpetuating the devastating impact of this pandemic.

A new approach to global vaccination, one that aims to achieve rapid, global epidemic control and eventual elimination, must be implemented. **Such an approach should achieve three primary objectives:**

HIT HARD

The world must prioritize the development of *highly effective* vaccines. A more effective vaccine not only reduces the risk of vaccine-resistant variants, but also provides more positive population level impacts when less of the population has been vaccinated compared with a less effective vaccine. Vaccine efficacy must also be considered in context, with specific attention to ease of distribution and administration in global settings.

Global production capacity previously dedicated to less effective vaccine candidates should be rededicated to more effective candidates. Furthermore, the world must build capacity on flexible vaccine platform technologies that can rapidly develop and produce "boosters" or new versions of the vaccine to combat new virological variants.

HIT FAST

Given the widespread nature of this outbreak, the faster a large portion of the population can be vaccinated, and transmission reduced, the more lives will be saved. Not only is hitting fast critical to saving lives, but it also gives the virus less time to evolve resistant variants.

HIT GLOBALLY

SARS-CoV-2 is a global pandemic. Rapidly reducing transmission everywhere is critical to reducing forward infections and the development of resistant variants. Already, vaccine resistant variants first detected in South Africa and possibly Brazil have been subsequently detected in other nations, including the United States.¹³ People in any one country will not be protected unless transmissions are halted globally.

The United States has a unique opportunity to re-establish global public health leadership by increasing mRNA vaccine capacity and ensuring rapid global immunization. Utilizing a public production model and contract manufacturing organization, the United States can partner with Moderna and build new mRNA vaccine manufacturing capacity to produce enough vaccine doses for the entire world in a single year (16 billion doses per year). Such a plan would cost less than \$4 billion – less than the U.S. government spends on COVID-19 response daily¹⁴ – and allow for production at approximately \$2 per dose.¹⁵ In doing so, the United States can address global vaccine shortages while building good-will on the world stage.

This document demonstrates how rapid United States based scale up of the NIAID/Moderna vaccine can propel global immunization, thereby reducing the threat of vaccine resistant variants, promoting global economic recovery, and saving countless lives. First, it details why an epidemic control and elimination approach is necessary, what factors make for an ideal vaccine candidate, and what outstanding research is needed. It then evaluates current vaccine technologies and explains why the NIAID/Moderna vaccine is the most promising candidate for scale up. Finally, it explains how the United States could rapidly increase production capacity for the NIAID/Moderna vaccine and what impact this would have on both the domestic and global pandemic.

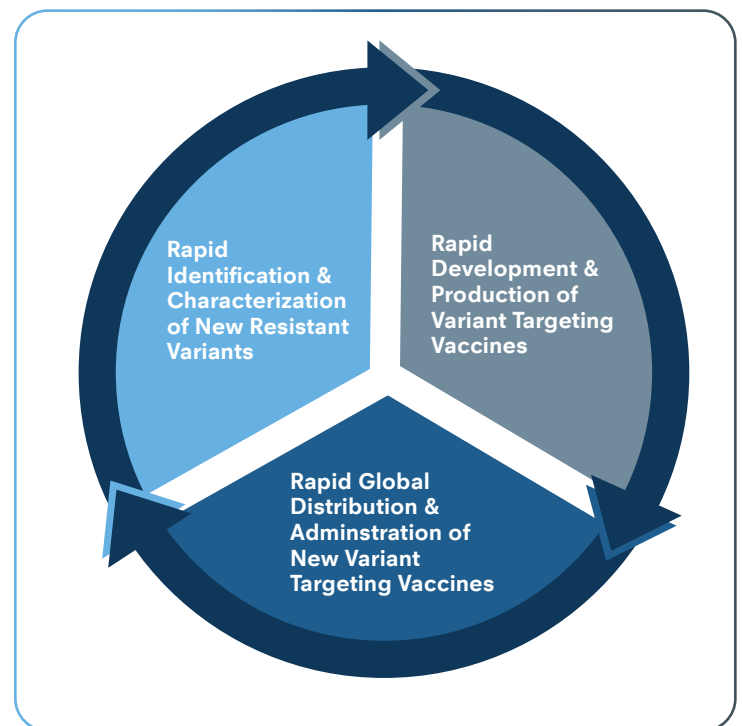


VACCINE EFFICACY AND EPIDEMIC CONTROL AND ELIMINATION

The purpose of an epidemic control and elimination strategy is to halt and prevent the population level transmission of a pathogen. Epidemic control and elimination means that even when new cases of a pathogen are introduced into a population, it is unable to spread widely. Epidemic control and elimination has been achieved for many pathogens, albeit with uneven progress geographically. For example, nearly universal global vaccination for polio has brought the spread of that pathogen under control and the epidemic eliminated in most populations — less than 40 cases of wild polio were reported worldwide in 2018.¹⁶ Achieving epidemic control allows any newly detected or introduced cases of the pathogen to be aggressively investigated, and other interventions (like booster vaccinations and contact tracing) to be initiated if necessary, ensuring the cessation of further transmission. Epidemic control can allow **epidemic elimination**, which is defined as the lack of any transmission of a pathogen within a given population after a defined period since the detection of the last index case (suggested to be not less than 3 months for SARS-CoV-2).⁵

Epidemic control and elimination are distinct from **pathogen eradication**, in which no individuals are infected with the pathogen worldwide and there is zero global transmission of the pathogen. While humanity has achieved epidemic control and elimination for many pathogens, it has only eradicated a single pathogen that infects humans, smallpox — with the last case being detected in 1977 and declared eradicated in 1980.¹⁷ Another pathogen, rinderpest (which only infects cattle and other ungulates — not humans), has also been eradicated.¹⁸

When using a vaccine or vaccines to help achieve epidemic control, estimating the **critical vaccination**



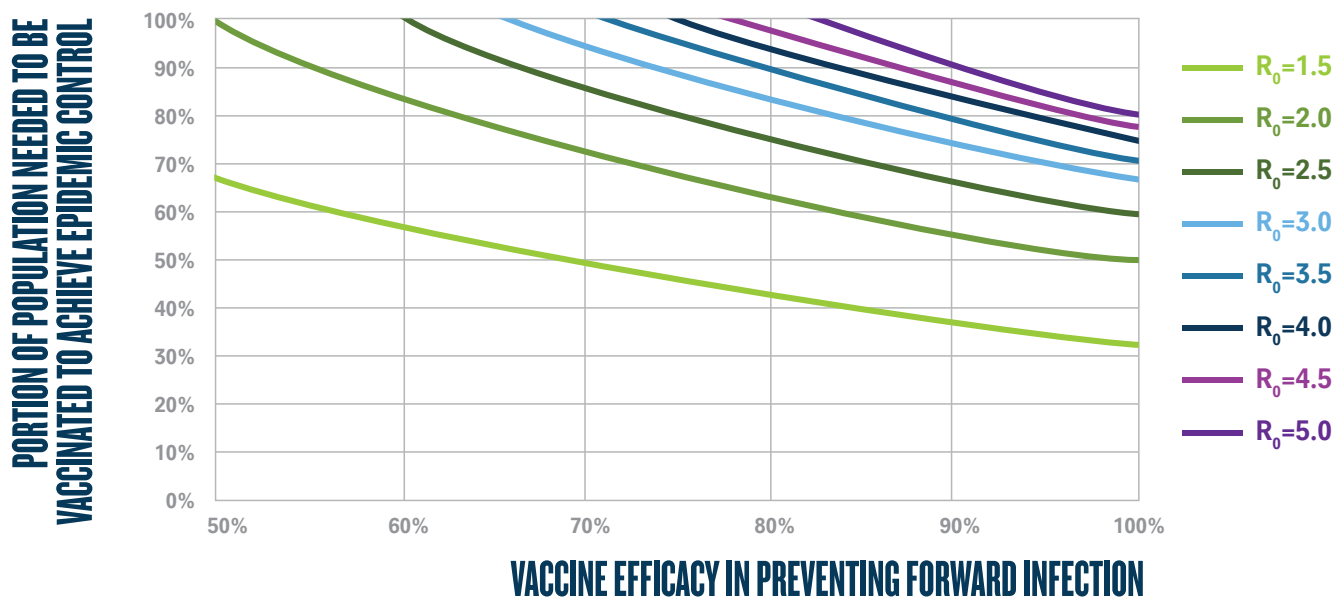
threshold (q_c) is vital. The critical vaccination threshold measures the minimum portion of the population that must be vaccinated to control the epidemic — that is, to bring the **effective** reproduction number (R_t) below one — meaning that an infected individual, on average, generates less than one secondary infections over the course of their infection, thereby achieving what is commonly referred to as “herd immunity”. The critical vaccination threshold depends on two factors — first, the efficacy of the vaccine in preventing forward transmission (E) and second, the **basic** reproduction number (R_0). The basic reproduction number measures, on average, the number of new infections a single infected individual generates in a **completely susceptible population** with no epidemic control measures or population level immunity in place. The higher the R_0 , the more

effective a vaccine must be and/or the larger the number of people must be vaccinated to reach herd immunity.

Mathematically, we can approximate the critical vaccination threshold by the following equation¹⁹:

For COVID-19, the basic reproduction number in higher income countries is commonly thought to lie between 2 and 4, with a point estimate of 3.8 being commonly used.^{20,21} It is important to note that this estimation of the critical vaccination threshold is an **approximation**, and certain assumptions are made. Most importantly, it assumes the cessation of all other epidemic control measures (like masking). Thus, it should be treated as a **conservative** estimate of the minimum portion of the population that needs to be vaccinated to achieve herd immunity.

IMPACT OF VACCINE EFFICACY AND BASIC REPRODUCTION NUMBER (R_0) ON THE CRITICAL VACCINATION THRESHOLD



VACCINATION HERD IMMUNITY THRESHOLDS FOR VARIOUS R_0 AND VACCINE EFFICACY ESTIMATES

VACCINE EFFICACY	R_0	2	2.5	3	3.5	4
50%		100%	Not Possible	Not Possible	Not Possible	Not Possible
60%		83%	100%	Not Possible	Not Possible	Not Possible
70%		71%	85%	95%	Not Possible	Not Possible
80%		63%	75%	83%	89%	94%
90%		56%	67%	75%	79%	83%
100%		50%	60%	67%	71%	75%

As demonstrated above, the ability of a vaccination program to impact community spread is highly dependent on how effective the vaccine is at stemming transmission of COVID-19. This is distinct from the ability of the vaccine to prevent illness or death. While a vaccine that is highly effective at preventing severe illness or death but not preventing infection and transmission (like the Johnson and Johnson vaccine), is obviously useful to the individual who is vaccinated, it is a less ideal candidate for a vaccination program that aims to achieve epidemic control.

Importantly, the ability of vaccines to prevent infection is distinct from the vaccine efficacy measured in most phase 3 COVID-19 vaccine trials. Most phase 3 COVID-19 vaccine trials, like those used for the Pfizer/BioNTech and Moderna/NIAID vaccines, measured the efficacy of the vaccine preventing symptomatic disease, not infection.^{22,23} Transmission from asymptotically infected individuals may represent a large portion of forward SARS-CoV-2 transmissions.²⁴ Preliminary evidence supports the conclusion that mRNA vaccines are highly effective in preventing both

SARS-CoV-2 infection and symptomatic disease, even after a single dose.²⁵

Measuring a vaccine's ability to prevent both symptomatic and asymptomatic transmission is imperative to understanding what portion of the population must be vaccinated to achieve epidemic control – and whether that vaccine can achieve epidemic control at all. For example, the AstraZeneca/Oxford vaccine's 70% efficacy in preventing infection likely cannot achieve epidemic control, in the absence of other epidemic control measures, even if 100% of the population were vaccinated. While asymptomatic transmission is being measured for some vaccine candidates – for example Israeli and American efforts to measure the ability of the Pfizer/BioNTech and Moderna mRNA vaccine to prevent both asymptomatic and symptomatic infection in “real world” settings²⁶ – a more coordinated, rapid approach is needed for all vaccine candidates which are being considered for production scale up.

RESEARCH RECOMMENDATION #1

A global coordinated research effort should be undertaken to ascertain COVID-19 vaccines' abilities to prevent not just symptomatic disease, but also forward transmission.

Even using symptomatic COVID-19 as an endpoint, many current vaccines are unable to achieve epidemic control even if one hundred percent of the population is vaccinated. As seen above in table 1, if no other epidemic control measures are in place, a vaccine with a minimum efficacy of approximately 80% in preventing forward transmission is likely needed. Peer reviewed results from more sophisticated compartmentalized mathematical modeling of COVID-19 transmission support this conclusion.²⁷

Vaccine efficacy is not the only criterion that should be used in selecting vaccine candidates for scale up. A more efficacious vaccine that is difficult to transport, store, and administer in the real world – conditions that could prevent a significant number of people from being vaccinated – may be less useful than a less efficacious vaccine that is easy to transport and administer. Thus, a careful balance must be made between theoretical efficacy and ease of actual use.



COMBATING ANTIGENIC DRIFT

“ It’s our wits versus their genes. ”

— J. LEDERBERG (1925-2008)

A key goal of a “hit hard, hit fast, hit globally” strategy is to reduce the development and spread of vaccine or natural immune resistant variants of SARS-CoV-2. By rapidly reducing transmission of SARS-CoV-2, and therefore, the number of people infected with the virus, the rate of viral evolution in response to immune or other selection pressures can be significantly reduced. Viruses cannot mutate without a host in which to replicate. Furthermore, by scaling up highly effective vaccines, the chance of the virus evolving in response to vaccine elicited immunity is further reduced.

RNA viruses like influenza and HIV generally have a high mutation rate. While coronaviruses have a significantly lower mutation rate than other RNA viruses^{28,29} the mutation rate of SARS-CoV-2 is still significantly higher than most cellular organisms and DNA viruses.³⁰ Seasonal circulating coronaviruses’ abilities to reinfect previously infected hosts is now thought to result from viral evolution in response to infection elicited immunity.³¹

Although SARS-CoV-2 vaccination efforts are nascent, substantial evidence has emerged that antigenic drift will challenge any epidemic control strategy. The resurgence of COVID-19 in Manaus, Brazil in January 2021 illustrates these challenges. Although 76% of the population was thought to have already been infected by October 2020 — suggesting levels of post infection immunity at or near the level required for epidemic control — a dramatic and rapid increase in COVID-19 infections, associated hospitalizations, and deaths was documented in January 2021. While the cause must be further explored, it is highly likely that viral strains resistant to naturally acquired immunity played a significant role.³²

Even the most aggressive vaccination campaign cannot fully prevent the development of new vaccine-resistant variants of SARS-CoV2, and newly discovered strains of the virus already appear to substantially reduce the efficacy of multiple COVID-19 vaccines. For example, the Novavax inactivated subunit vaccine was found to be 89% effective in preventing symptomatic COVID-19 in the United Kingdom but was less than 50% effective in South Africa.³³ Similarly, the AstraZeneca/Oxford vaccine showed approximately 70% efficacy in the UK, but less than 30% efficacy in South Africa.³⁴ These efficacy reductions are likely due to a viral variant (known as 501Y.V2 or B.1.351) that is in widespread circulation in South Africa. Importantly, vaccinations had not yet begun in South Africa outside of clinical trials when the Novavax trial was taking place. This example highlights the likely role **infection-elicited** immunity plays in conferring resistance to **vaccine-elicited** immunity.

New versions of vaccines must be created to target vaccine resistant variants. Thus, global production forecasts, which already show significant vaccine shortages persisting for years, likely **underestimate** the extent of the problem. Previously immunized populations will likely need to be **revaccinated** to combat newly resistant variants, exacerbating existing shortages.

Antigenic drift will be a challenge to any epidemic control strategy — including ones that do not rely on vaccination at all. Overcoming it relies on two critical factors — first, the ability to rapidly **detect** the emergence of new variants and, second, the ability to rapidly **manufacture and deploy** highly effective vaccines that can combat new variants.

POLICY RECOMMENDATION #1

The world must dramatically increase its surveillance capacity for new SARS-CoV2 variants. It should aim to sequence 1% of all new cases globally – in a geographically unbiased fashion – within 7 days of diagnosis. By doing so, new versions of vaccines that prevent transmission of new viral variants can be rapidly developed.

Rapid genetic sequencing can help detect new variants that may confer transmission or other evolutionary advantages. Sequence information and epidemiological information can be analyzed *phylogenetically*,³⁵ which allows for the rapid detection of viral variants that may affect vaccination efforts and other epidemic control measures. This method allowed the detection of the B.1.1.7 variant in the United Kingdom, which is thought to be more contagious than other strains of SARS-CoV2. It also allowed detection of the 501Y.V2 variant in South Africa, which is thought to be partially resistant to current vaccines.

Fortunately, the rapid detection of the 501Y.V2 variant has empowered manufacturers to begin producing new versions of their vaccines to combat this variant.³⁶

Currently, viral genomic sequencing has been performed on less than a half a percent of diagnosed COVID-19 cases – with huge geographic disparities in sequencing coverage. Failure to increase and diversify sequencing geographically will allow new variants to spread undetected for a substantial period, thus increasing the time to develop and produce new versions of a vaccine.

POLICY RECOMMENDATION #2

Ample vaccine production capacity must be created to produce not only enough vaccine to vaccinate the global population once but also rapidly combat new resistant variants. Vaccine platforms that are amenable to multiple sequential booster injections should be prioritized.

Epidemic control may require multiple vaccinations per person, with 'booster' shots providing protection against new variants. Sufficient vaccine production capacity must be created to rapidly produce new booster shots

for the global population. Furthermore, vaccines should be assessed for their ability to induce protection after multiple shots (i.e., more than just two).

RESEARCH RECOMMENDATION #2

Factors that may reduce booster vaccines' abilities to elicit protective immune responses should be characterized for all current COVID-19 vaccines.

Although vaccines are intended to induce a protective immune response to a pathogen like SARS-CoV2, certain vaccines can also elicit immune response to components of the vaccine **itself**. This is particularly concerning for adenovirus vector vaccines such as the Johnson & Johnson, AstraZeneca/Oxford, and Sputnik V COVID-19 vaccines, where immunity to the adenovirus vector ('anti-vector immunity') can inhibit a protective immune response to the antigen coded for by the vectored vaccine.³⁷

Given the likely need for booster shots to combat COVID-19, studies must be undertaken urgently to determine which COVID-19 vaccine technologies induce strong anti-vaccine immune responses that may preclude subsequent booster shots. In addition, other strategies such as heterologous boosting (i.e., using different types of vaccines for subsequent boosting) should be investigated.

RESEARCH RECOMMENDATION #3

Centralized research facilities should be created that can evaluate newly discovered viral variants *in vitro* and animal models.

Once phylodynamic surveillance detects the potential spread of a new SARS-CoV2 variant, researchers must be able to rapidly characterize potential biological differences in the variant to help determine its threat to epidemic control efforts. Traditionally, this would require

transporting a patient specimen to a laboratory to reproduce and characterize the variant; however, modern molecular biology techniques allow for the reproduction of the variant using its whole genome RNA sequence without the need for a patient specimen.



COVID-19 VACCINE TECHNOLOGIES

Not all COVID-19 vaccine candidates are equally suited for global scale up.

Any effective vaccination strategy must rapidly identify new vaccine resistant viral variants and design, develop, mass produce, and deploy new vaccines or vaccine “boosters” that confer immunity to these variants. An ideal vaccine candidate will have the following characteristics:

- **It is highly efficacious at preventing transmission of COVID-19 and severe COVID-19 disease.**
- **Its manufacturing process is easy to scale up rapidly.**
- **Its manufacturing process is easily adaptable to combat new variants as they emerge.**
- **It has good cold-chain characteristics, i.e. it can be stored at regular refrigerator and freezer temperatures for extended periods of time.**
- **It is easy to distribute and administer on a global scale.**

Despite the large number of vaccines under development, they all use one of four vaccine technologies to elicit an immune response: inactivated whole virus, protein subunit, adenoviral vector, and mRNA-based vaccines. This section provides a brief overview of each vaccine technology and how they work. A more detailed analysis of each vaccine technology can be found in the appendix.

INACTIVATED WHOLE VIRUS VACCINES

Inactivated whole virus vaccines consist of whole SARS-CoV-2 viral particles (known as “virions”) produced in cell culture and rendered non-infectious via treatment with special chemicals – a process known as inactivation. The necessity of bringing up whole virus in cell culture represents a possible barrier to rapid switching to produce new variant targeting booster shots. Other inactivated whole

virus vaccines include Jonas Salk and colleagues’ polio vaccine and most influenza vaccines. An inactivated whole virus cannot induce a CD8+ T-cell response, unlike mRNA or adenoviral vectored vaccines, due to its inability to induce expression of viral proteins within the cell. Two primary inactivated vaccines, BBIBP-CoRV (from Sinopharm) and CoronaVac (from Sinovac), have completed phase 3 clinical trials. The largest phase 3 clinical trial to evaluate CoronaVac showed a low efficacy of 51% in preventing symptomatic COVID-19.³⁸ Sinopharm claims that BBIBP-CoRV is 79% effective in preventing symptomatic COVID-19, but in a remarkable deviation from international norms, has refused to release even the most basic details about how this number was derived.³⁹

Advantages

- Able to utilize existing infrastructure of large-scale bioreactors for production.
- Both vaccines can be stored and distributed at normal refrigerator temperature.⁴⁰

Disadvantages

- Unclear efficacy.
- Requires biosafety level 3 biocontainment facilities for production of SARS-CoV-2 virions and downstream processing until after the inactivation step.
- Likely difficult for manufacturing process to produce vaccines that can combat new variants.
- Production process depends heavily on large scale mammalian cell culture.

PROTEIN SUBUNIT VACCINES

Protein subunit vaccines work by injecting the patient with protein components (or “subunits”) of the pathogen that function as antigens. Proteins are

produced recombinantly in cell culture. Other protein subunit vaccines include hepatitis B vaccines and human papilloma virus (HPV) vaccines. The leading protein subunit vaccine, developed by Novavax, uses an engineered version of the spike protein of SARS-CoV-2 as an antigen. Only the **Novavax** inactivated vaccine has released phase 3 efficacy data. Interim phase 3 data from a trial in the United Kingdom (n>15,000), showed **89.3% (95% CI: 75.2 – 95.4) in preventing symptomatic COVID-19** – with 6 cases in the Novavax group compared to 62 cases in the placebo group.⁴¹ In South Africa, preliminary results from a phase 2b trial showed a remarkable reduction in efficacy at only **49.4% (95% CI: 6.1 – 72.8)**. This reduction was presumably due to the 501Y.V2 viral variant that is spreading in South Africa. While the Novavax vaccine is highly efficacious in preventing non-resistant COVID-19, the manufacturing process's heavy reliance on cell culture makes it possibly slower in adapting to new variants.

Advantages

- Able to use existing bioreactor capital infrastructure for recombinant protein production, at normal biosafety conditions (BSL2).
- Highly efficacious against non-escape variants of SARS-CoV-2.
- Good cold chain characteristics (4°C for more than six months).

Disadvantages

- Highly dependent on complex tissue culture processes for manufacturing, complicating generating new versions of the vaccine to combat new virus variants.
- Tissue culture processing requires extensive capital infrastructure for both generation of the protein and subsequent downstream processing.

ADENOVIRUS VECTORED VACCINES

Adenovirus vectored vaccines work by genetically modifying an **adenovirus** – a family of common cold viruses – to deliver DNA that codes for the vaccine antigen inside human cells.⁴² To transform adenovirus into an adenovirus vector, portions of the viral genome that allow the virus to replicate are deleted. This produces **replication incompetent vectors** – which cannot replicate within the immunized individual but can still deliver the antigenic gene into the patient being immunized. Adenovirus

vaccines utilize complex cell culture processes for production. A significant downside for adenoviral vectored vaccines is anti-vector immunity, where the vaccinated individual mounts an immune response to the vector as well as the antigen it codes for. This could preclude the use of the same adenoviral vector to inoculate against new variants in individuals who were immunized with the same vector.

The **AstraZeneca\Oxford Vaccine, AZD1222**, uses a replication incompetent simian adenovirus (ChAd) serotype Y25 (ChAdOx1) vector and is also being produced under license by Serum Institute. It showed a **70.4% efficacy (95% CI: 41.0 – 75.7)** in preventing symptomatic COVID-19 following two doses of the vaccine. Concerningly, recently released data from South Africa showed an extraordinarily low efficacy (below 25%) of the vaccine preventing COVID-19 disease, presumably due to the variant spreading there.

The **Johnson and Johnson vaccine, JNJ-78436735**, using a replication incompetent adenovirus type 26 (Ad26) vector, **showed efficacy of 72%** in preventing moderate to severe COVID-19 in the United States, 66% in Latin America and 57% in South Africa, after a **single dose**.⁴³ These results have not been peer-reviewed and confidence intervals have not been provided. JNJ-78436735 uses a pre-fusion conformation stabilized full-length SARS-CoV-2 spike protein as its antigen, like the Moderna\NIAID, Novavax, and Pfizer vaccines.

The **Gamaleya Research Institute of Epidemiology and Microbiology's vaccine, Sputnik V**, utilizes two distinct replication incompetent adenovirus vectors, adenovirus type 26 (Ad26) as the first or "prime" dose, and adenovirus type 5 (Ad5) as the second or "boost dose" – a "heterologous prime boost" approach. This vaccine **was 91.6% (95% CI 85.6–95.2)** effective in preventing symptomatic COVID-19 disease.⁴⁴ No data is available from countries, like South Africa, with vaccine resistant strains circulating. The use of adenovirus type 5 (Ad5) boost vector is concerning, given the association of that vector, in multiple clinical trials, with increased rates of HIV infection.⁴⁵ Unfortunately, none of the clinical trials evaluating Sputnik V have reported safety data on HIV risk.

Advantages

- Good temperature characteristics (all leading candidates can be stored for at least three months at 2-8°C).
- At least one adenoviral vector vaccine, JNJ-78436735, was effective as a single dose.

- Can utilize existing bioreactor manufacturing capacity.

Disadvantages

- Extremely complex manufacturing process that will likely pose a significant barrier to production of both initial and new variant booster products.
- Extremely high dose (10^{10} to 10^{11} vector particles per shot) required, further complicating manufacturing.
- Unlikely to be able to use the same vector for new variant boosters in previously immunized individuals, due to anti-vector immunity.
- Safety risks with certain adenoviral vectors, like Ad5.

mRNA VACCINES

The mRNA vaccine production process is distinct from other vaccine technologies in that the production process is almost entirely **cell free** — meaning that production is not dependent on cell culture-based manufacturing processes, but instead on synthetic processes that are far more flexible in production scale up.

The vaccine from a collaboration between Pfizer and BioNTech, known as **tozinameran, showed 95% efficacy (95% CI:90.3 – 97.6) in preventing symptomatic COVID-19 in a large phase 3 randomized control trial after two doses.**⁴⁶ No information is available about the efficacy of the vaccine in countries where resistant variants are circulating. Preliminary evidence supports the ability of the vaccine to reduce transmission on a population scale,⁴⁷ reduce the viral load of infected individuals soon after the first dose of vaccine,⁴⁸ and be efficacious after a single dose.

mRNA-1273, a vaccine developed by a collaboration between NIAID and Moderna, **showed a 94.3% efficacy in preventing symptomatic COVID-19.**² No information is available about the efficacy of the vaccine in countries where resistant variants are circulating.

Advantages

- Extremely efficacious candidates.
- Extremely rapid manufacturing process – proven ability to rapidly scale.
- Nearly cell free manufacturing process allows rapid development and production of new vaccines to combat new variants.

Disadvantages

- Cold chain characteristics less than ideal (NIAID\ Moderna's candidate can only stay at 4°C/40°F for 30 days, otherwise regular freezer temperatures -20°C/40°F are required).
- Pfizer\BioNTech's candidate requires -70°C/-94°F for storage.
- Limited standby manufacturing capacity, due to novelty of mRNA vaccines.

SELECTING A VACCINE TECHNOLOGY FOR SCALE UP

The vaccine developed by NIAID and Moderna is the best candidate for rapid global scale up. It is highly effective at preventing symptomatic COVID-19, meaning it can achieve epidemic control with a smaller proportion of people vaccinated than other candidates. mRNA vaccines are also easier to rapidly scale than other vaccine technologies, largely due to their nearly cell free manufacturing process. Indeed, global commercial manufacturing capacity for mRNA vaccines grew from precisely zero in February to well over a billion doses per year in December, with most production lines being built within existing pharmaceutical plants and becoming operational in six months or less. This cell free manufacturing process also makes it easier to adapt to new variants than other vaccine technologies, giving it an advantage for combatting emerging viral variants.

Although existing mRNA vaccines' cold chain characteristics are less ideal than other technologies, the vaccine developed by NIAID and Moderna can be stored at regular refrigerator and freezer temperatures, which are generally available in LMICs. The Pfizer/BioNTech vaccine has much more challenging cold chain characteristics, making it more difficult to distribute and administer. For this reason, the NIAID/Moderna vaccine should be prioritized over the Pfizer/BioNTech vaccine.

Adenoviral vectored vaccines currently represent the bulk of planned production capacity for 2021; however, these candidates are particularly ill-suited to combating new variants. They are difficult and slow to both manufacture and adapt to new variants. Additionally, adenoviral vectored vaccines induce an immune response to the adenoviral vector itself in addition to the antigen(s) they code for. Once vaccinated with a particular adenoviral vector, a person is likely precluded from being boosted using

the **same adenoviral vector** to induce immunity to a new variant.

Importantly, one cannot simply “switch” to a different adenoviral vector for subsequent booster shots. Only a few adenoviral vectors exist that human populations are not already immune to. In addition, each new vector must be rigorously evaluated in new clinical trials to demonstrate both safety and efficacy. Previous experience with adenoviral vectored vaccines shows that significant safety issues can arise when using new vectors. For example, two randomized control trials for two different Ad5 adenoviral vectored HIV vaccines demonstrated an increased HIV acquisition risk in individuals who were immunized, likely due to the use of the Ad5 vector itself.

Without access to basic data surrounding both Sinopharm and Sinovac’s inactivated whole virus vaccines, it is impossible to independently verify their efficacy. Until that data is released, such vaccines should not be considered for global scale up. Protein subunit vaccines, however, have proven highly efficacious in phase 3 clinical trials, at least in countries where resistant variants are not predominant. Despite this, mRNA vaccines nearly (or entirely) cell free manufacturing process poses a critical advantage to both inactivated whole virus vaccines and protein subunit vaccines. The cell free manufacturing process allows commercial production to rapidly switch to vaccines targeting new variants

— estimated to take less than six weeks. On the other hand, protein subunit vaccines and inactivated whole virus vaccines require a complex recombinant protein production process utilizing tissue culture. Furthermore, mRNA vaccines can induce a CD8+ T-cell response, which may be crucial in providing vaccines with a higher genetic barrier of resistance to viral variants. Neither protein subunit vaccines nor inactivated whole virus vaccines induce such a response.

Current combined production plans for both the Moderna\NIAID and Pfizer\BioNTech mRNA vaccines, even in the most optimistic production forecasts, will only produce 3 billion doses — enough for 1.5 billion people — in 2021. As a new technology, mRNA vaccines use a unique manufacturing process distinct from all other vaccine and commercially approved drugs. Thus, there is no “slack” manufacturing capacity available that can be repurposed to increase production. New capacity must be built. Fortunately, new mRNA vaccine manufacturing capacity can be built rapidly. Before February 2020, **no** commercial scale capacity existed. In less than a year, private industry, with multi-billion-dollar investments from the U.S. Government and other governments, successfully built billion dose plus per year capacity.



ACHIEVING GLOBAL VACCINATION IN 2021

The world's current vaccination strategy is ill-suited to the task of global COVID-19 epidemic control.

Current production forecasts estimate that widespread global vaccine access will not occur until 2023, a delay that threatens not only those in mostly middle- and lower-income countries, but all people in all nations. Failing to rapidly vaccinate the global population will allow the virus to continue spreading at large scale and allow the ongoing development of vaccine-resistant variants that are already having negative public health and economic consequences in much of the world.

To achieve epidemic control and to enable rapid control of vaccine-resistant variants, the world should aim to produce 16 billion doses per year – enough for the entire global population to be vaccinated once per year. The United States can create **publicly owned** production capacity to do this. Then, it can contract with the original vaccine manufacturer (e.g., Moderna) for use of the know-how, manufacturing processes, and relevant underlying intellectual property to produce the vaccine.

Such an approach has numerous advantages:

- By contract manufacturing, a publicly owned vaccine manufacturer facility can produce the exact same version of the vaccine, averting the need for new clinical trials evaluating the safety, immunogenicity, and efficacy of vaccines manufactured through other licensing approaches.
- By utilizing public manufacturing, the immense capital and legal resources of the government can overcome both capacity and supply chain issues.
- Finally, public ownership ensures that taxpayer investment in manufacturing capacity will leave the nation better prepared for the next pandemic – regardless of the original manufacturer of the relevant mRNA vaccine – by enabling rapid domestic production of future vaccines at scale that can also cover global need.

This section outlines how the United States would build such capacity as fast as possible, with commercial production beginning in six months or less after implementation. Our proposal targets the NIAID/Moderna mRNA vaccine (i.e., mRNA-1273 and its derivatives), a vaccine as efficacious as Pfizer/BioNTech's mRNA version with the crucial difference that it can be stored at normal freezer and refrigerator temperatures. Although the proposal is tailored to the U.S. government, it can be readily adapted to other governments. The U.S. government can repurpose existing facilities or build new ones to create such capacity, while also using its unique statutory powers, like the Defense Production Act and government patent use under 28 U.S.C. §1498.

Critically, the U.S. government already owns key aspects of the intellectual property protecting the NIAID/Moderna vaccine since NIAID played a critical role in inventing it. However, components of the vaccine are likely protected by intellectual property that Moderna – or another company – owns outright. Furthermore, Moderna and other companies have developed critical know-how on the manufacturing processes for the vaccine. If the federal government uses such knowledge, it should compensate Moderna and any other respective companies for doing so.

In many pandemics, for example HIV, robust generic markets for brand-name drugs facilitate global access to critical small-molecule drugs in LMICs, often before patent-based exclusivity for these drugs expires. Generic drugs are versions of brand-name ones that contain the same active ingredient(s), and in the same dosage, but are made by a different manufacturer. Once regulatory authorities certify that a given generic drug is therapeutically equivalent to the brand-name drug, they can be used interchangeably. Critically, manufacturers of generic versions are not required to repeat clinical trials to establish safety and efficacy, which rapidly reduces the time to approval for generic versions of a drug. By ensuring multiple manufacturers of a given drug, generic competition allows both robust supply and low costs – for example, reducing the cost of HIV treatment from tens

of thousands of dollars per year to under a hundred dollars per year.

Unlike small molecule drugs, however, no pathway exists for a manufacturer to make a generic version of a different company's brand-name vaccine. The lack of generic vaccines poses a serious barrier to vaccine access, even in cases where there are no patents protecting the vaccine or the intellectual property is licensed to another manufacturer. For example, both AstraZeneca and Novavax have licensed their respective COVID-19 vaccines to the Serum Institute of India (one of the world's largest vaccine manufacturers) so that Serum can manufacture its own versions of those companies' vaccines. However, despite extensive collaboration between the two companies and Serum, Serum Institute still must run its own large trials (more than 1,000 persons each) for its version of the AstraZeneca and Novavax vaccines — it cannot rely exclusively on the existing clinical trials. The need for these 'bridge clinical trials' dramatically slows down the ability of using licensed manufacturers to increase supply.⁴⁹

However, a distinct manufacturing approach called contract manufacturing can enable rapid production scale up without the need for repeating clinical trials. Indeed, this approach allowed Moderna, a then-small biotech company, to scale up production of its COVID-19 vaccine to a billion dose per year capacity. More than 80% of Moderna's vaccine drug substance is not made by Moderna, but rather by another company, Lonza Group AG, which makes it under contract for Moderna.⁵⁰ In contract manufacturing, a brand-name company signs an agreement with another company, called a contract manufacturing organization (CMO), to produce drug substance or provide other manufacturing services. The CMO then produces the drug substances using the exact same production processes and quality control measures as the brand-name company, and the brand-name company markets the CMO-produced product under its regulatory authority (i.e., the brand-name company's license or emergency use authorization).

Today, Lonza, not Moderna, owns and operates factories in New Hampshire and Switzerland to produce drug substance for more than 80% of Moderna's distributed mRNA-1273 doses. After Lonza produces the drug substance, other CMOs, including Catelant, Inc. and Laboratorios Farmaceuticos ROVI SA (ROVI), put the vaccine product into vials, package it, and freeze for distribution.

Public manufacturing would utilize a similar model. By creating a government-owned CMO, the federal government could rapidly build both drug substance

and product production capacity, as well as fill-finish capacity. Moderna and the U.S. government would then enter a contractual relationship allowing the government-owned CMO to produce the vaccine on the company's behalf, and under its licensing authorization.

The necessary intellectual property and know-how that the government does not already own would then be licensed through a subscription model. In a subscription model of intellectual property licensing, the federal government would pay Moderna a fixed amount per year for the use of its intellectual property, rather than a per dose royalty fee. In return, Moderna would authorize the federal government to produce as much vaccine as possible. This decouples the unit price of the vaccine dose from the royalties on the intellectual property, allowing the vaccine to be sold at the price of production. This could allow the U.S. government to sell or donate the vaccine at the cost of production — around \$2 a dose — to LMICs directly or to multilateral vaccine distribution facilities such as COVAX.

Centralizing drug substance production in a single CMO (in this case, a federally owned one) substantially reduces the logistical burdens of tech transfer. The process of tech transfer to scale up contract manufacturing for a vaccine is non-trivial and requires extensive collaboration between the originator company (Moderna) and the CMO. By creating a single CMO with extensive capital resources — which could make available virtually unlimited scale up capacity — this tech transfer process could be sped up and simplified, reducing the burden on the originator company. This process could be further simplified by hiring an experienced existing biopharmaceutical CMO (like Lonza itself or Emergent BioSolutions Inc.) to operate the government-owned CMO. This model of hiring highly experienced private companies to operate publicly owned facilities is used already by the U.S. Department of Energy to operate the nation's national laboratories (where companies like e.g., Bechtel, General Electric, and Battelle operate the labs on behalf of the government all but one).

SPEED AND COST

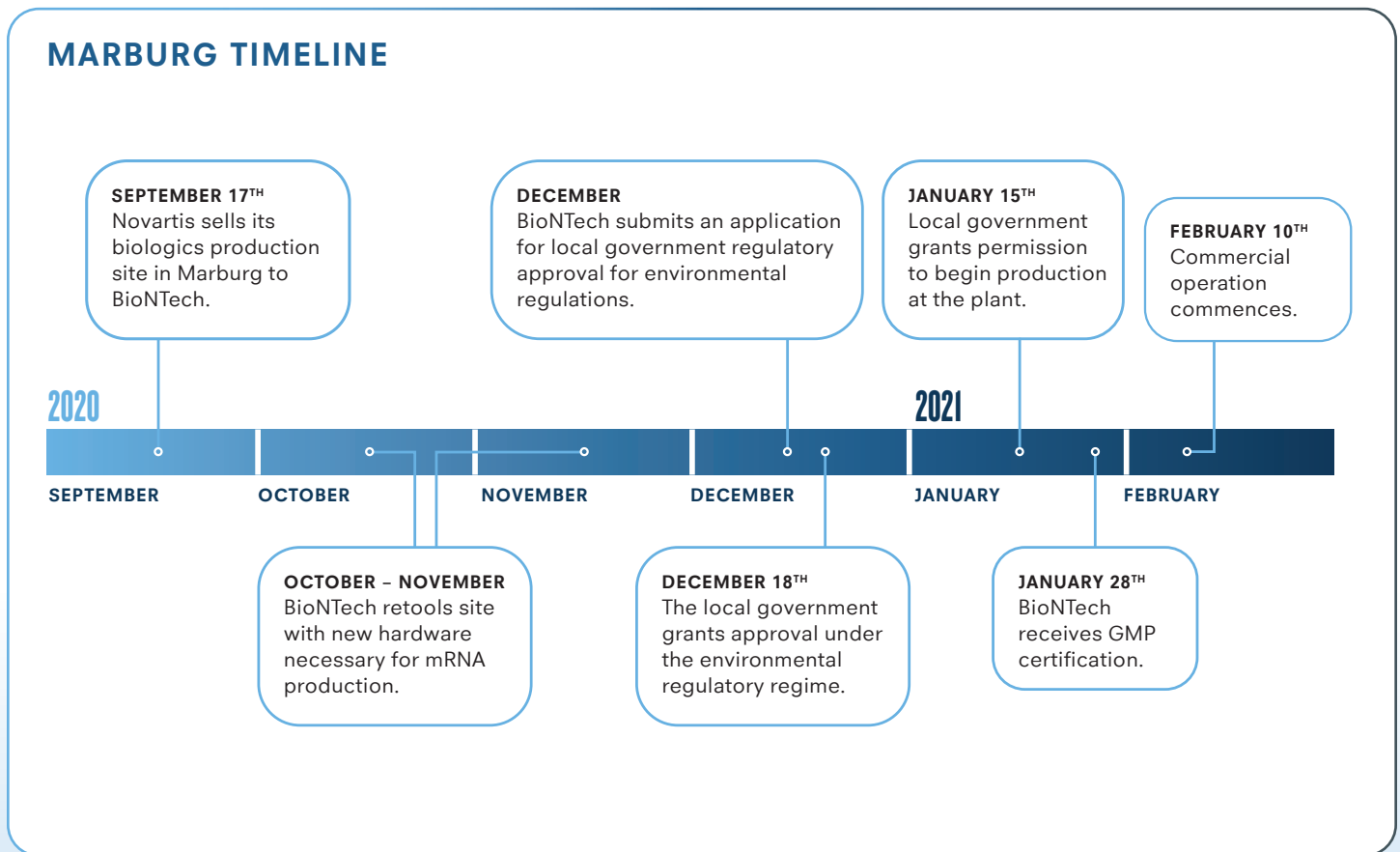
A critical objective of any effective SARS-CoV2 vaccine strategy is speed of production scale up. The production process advantages of mRNA vaccines over other vaccine platforms allow building, commissioning, and initiating commercial operation of a new mRNA vaccine production line rapidly — as

quickly as two to six months from commencement of construction. These advantages have been demonstrated repeatedly in the real world. For example, BioNTech bought a biopharmaceutical plant from Novartis International AG in Marburg, Germany on September 17, 2020 with no built-in mRNA vaccine production capacity.⁵¹ By February 10, 2021, the plant – which has the capacity to produce 750 million doses per year – began commercial operation.

Lonza’s scale up of production lines for the Moderna/ NIAID vaccine was similarly rapid. Lonza began tech transfer operations with Moderna in June 2020, and brought four new production lines, in Switzerland and New Hampshire, into commercial operation by November 2020.⁵² This rapid build time was achieved despite the production lines being ‘first of a kind’ (FOAK), as neither company had ever built a

commercial mRNA vaccine production line before. Presumably, with the experience gained from previous build experience, such production capacity could be brought online even faster.

Scientists and engineers from Imperial College-London estimate that the capital costs of a large facility with the capacity to manufacture a 16 billion doses per year of an mRNA vaccine like mRNA-1273 would cost \$3.9 billion to build. This is comparable to the actual cost of Lonza’s construction of the FOAK production lines in Switzerland and New Hampshire, which averaged USD \$78 million per line.⁵³ Each line can produce 100 million doses per year. Therefore, even assuming Lonza’s FOAK production line cost, scaling to 16 billion dose per year, would cost approximately US\$12.5 billion.



PHYSICAL PLANT REQUIREMENTS

Vaccines, like all pharmaceutical products, must be manufactured in facilities compliant with Current Good Manufacturing Practices (CGMP) as established by national and international regulatory authorities. mRNA vaccines are injectable products, so extreme caution must be taken to ensure sterility and protection from contaminants throughout the production process. Furthermore, the production of RNA itself is extremely sensitive to contamination. Thus, mRNA vaccine production, like all other vaccines, takes place in 'cleanroom' facilities, which utilize specialized heating, ventilation, and air conditioning (HVAC) equipment, generally with high efficiency particulate air (HEPA) filtration systems, to ensure extremely low levels of particulates and other contaminants within the facility.⁵⁴ The level of cleanroom necessary is dependent on whether the production process is open or closed. In an open production process, vessels or devices containing components of the finished drug substance product are open to the cleanroom environment, whereas in a closed production process, the finished drug substance is never exposed to cleanroom air.¹⁵ Neither Moderna nor Pfizer has disclosed whether its

production process is open or closed, although it is likely that the mRNA vaccine production is particularly conducive to closed production processes.

Lonza, Pfizer, and BioNTech have all repurposed existing pharmaceutical plants, presumably with built-in cleanroom capability, for their mRNA vaccine production facilities. It would be clearly preferable, from a speed perspective, that public production be done at an existing manufacturing plant with preexisting cleanroom facilities. It is important to note that other industrial facilities, like semiconductor fabrication facilities ('fabs'), possess high-grade cleanroom environments as well. Such facilities, if available for purchase or leasing, may also be amenable for rapid conversion to mRNA vaccine production.

However, plants of the necessary size and functionality that meet these ideal criteria may not be available for purchase or leasing. In such a scenario, we would need to rapidly build large cleanroom facilities to house the manufacturing processes. Historically, building cleanroom facilities has been both costly and slow, but the advent of modular cleanrooms — where different components (e.g., individual walls with built-in HVAC ducting), called 'modules', are fabricated at a specialized factory and then transported to the production facility to be assembled — has led to dramatic decreases in



The outside of an assembled modular cleanroom facility, built within an existing industrial building. Note the HVAC, plumbing and electrical interconnections between the cleanroom modules and the enclosing building.

COURTESY: G-CON MANUFACTURING.

POLICY RECOMMENDATION #3

The U.S. government should identify existing cleanroom facilities for potential procurement in the United States or around the world. If none are available, the U.S. government should invest in building modular cleanroom facilities within existing industrial buildings that can be rapidly repurposed.

the time to build a new cleanroom facility.⁵⁵ Modular cleanrooms can be assembled within an existing large building (like a warehouse or a conventional industrial facility) where the necessary mechanical, electrical and plumbing (MEP) services are available. This can allow the rapid transformation of ordinary vacant industrial spaces into functional pharmaceutical production facilities.

Modular cleanroom facilities can be built extraordinarily rapidly. A modular ISO class 7 cleanroom facility (equivalent to FED-STD 209E class 10,000, European Union CGMP grade 'C') can be built in under three months, from initial order to commercial operation at the production facility. A modular ISO class 5 cleanroom facility (equivalent to FED-STD 209E class 100, European Union CGMP grade 'A') – utilized for the most sensitive process in biopharmaceutical manufacturing, like open production processes – takes slightly longer, however can be built in under 6 months, from initial order to commercial operation.⁵⁶

OVERCOMING POSSIBLE SUPPLY CHAIN CONSTRAINTS

The production of mRNA vaccines utilizes several chemical components not commonly used in other commercial products. These components, utilized in the final finished drug substance or as intermediate substances for subsequent production processes, are known as 'feedstock', and ensuring a robust supply is critical to scale up of mRNA vaccine production.

While much has been written and said about these possible barriers, it is important to keep them in perspective. For a round of vaccination that will cover the entire global population (i.e., 16 billion doses), the total amount of modified RNA drug substance that needs to be produced is less than 2 metric tons, and the total amount of lipids in finished drug substance is approximately 30 metric tons. This is comparable to the amount of drug substance for complex biologic drugs like monoclonal

antibodies that is routinely produced by other areas of the pharmaceutical industry⁵⁷ and is orders of magnitude smaller than the amount of drug substance produced by the small molecule drug industry.

This report focuses on four possible feedstock barriers to mRNA vaccine production scale-up: template DNA, the synthetic 5' (pronounced five prime) cap, n1-methyl pseudouridine triphosphate [N1m Ψ (PO₄)₃], and the lipids used to manufacture the lipid nanoparticle (LNP).

Estimating the capacity needed for production of the template DNA, synthetic 5' cap, and N1m Ψ (PO₄)₃ requires knowledge of the modified RNA sequence of mRNA-1273. Unfortunately, Moderna has not released this information. The general lack of transparency by Moderna is inexplicable, especially considering the billions of dollars of public money invested in the development and manufacture of this vaccine. However, Pfizer/BioNTech has released its modified RNA sequence,⁵⁸ which was used instead as the basis of these calculations. Given these limitations, these estimates should be treated as rough, order of magnitude estimates for production requirements.

While extensive calculations are provided in the appendix, we estimate that the feedstock needs for all precursor and constituent components are likely within the ability of existing industrial capacity, or capacity that could be rapidly built and redirected to vaccine purpose.

Template DNA – the DNA component used to synthesize the modified RNA drug substance – needs are estimated at the order of 10 kilograms. Likely to be required for the other four key feedstock components are on the order of 10 kilograms of 5' cap, 10 metric tons of N1-methylpseudouridine triphosphate, and 20 metric tons of the cationic lipid SM-102. While this amount of feedstock components may be beyond existing industrial capacity, the federal government can use existing policy tools to ensure adequate supply of feed stock components.

POLICY RECOMMENDATION #4

The U.S. government create a Vaccine Production Board to rapidly assess the capacity of the existing suppliers for critical feedstock components.

The federal government should convene an emergency Vaccine Production Board, like President Biden's COVID-19 Pandemic Testing Board and President Roosevelt's War Production Board during World War II, to assess the capacity of existing suppliers to provide enough feedstock components for vaccine production scale-up. This should include recommendations to use the Defense

Production Act to prioritize providing sufficient vaccine feedstock supplies over other industrial needs, if needed, or to provide capital expenses to build more production capacity to supply vaccine production needs. Essential feedstock components that will not be able to be provided by existing suppliers should be rapidly identified.

POLICY RECOMMENDATION #5

The U.S. government utilizes open tendering with an explicit 28 U.S.C. §1498 authorization to source scarce feedstock components.

Robust small molecule active pharmaceutical ingredient (API) and excipient supply markets exist globally that have proven repeatedly to be able to rapidly sustain production of complicated small molecules for pharmaceutical use at the necessary quality and scale. Hypothetically, this industrial capacity could be utilized to make up for feedstock supply shortages that existing manufacturers cannot supply. However, the intellectual property protecting many of these components remains complex and may disincentivize smaller suppliers from attempting to supply these compounds, for fear of patent infringement liability.

The use of an existing federal law, 28 U.S.C. §1498, can remedy this issue. The law allows

the federal government to use any U.S. patent for any purpose and to provide a license to a third-party manufacturer to use those patents if the intellectual property is being used for the federal government.⁵⁹ This sweeping power immunizes third-party manufacturers from any patent infringement liability and shifts that liability to the federal government. Patent holders can get compensated for the government's use of their intellectual property if a federal court finds that their intellectual property has been infringed and that their patents are valid and enforceable. However, under the law patent holders cannot stop the use of their intellectual property by the government under any circumstances.



CONCLUSION

Without universal global access to vaccines, millions more people will die from COVID-19 in addition to the 2.2 million who had already been killed because of SARS-CoV2 infection by February 2021.

With current forecasts projecting that only 27% of people in LMICs will receive vaccines in 2021, the pandemic will continue largely unmitigated in these countries, which comprise more than three quarters of the world's population, for the foreseeable future. Not only will such a failure needlessly prolong the current public health crisis, but it also creates a breeding ground for vaccine-resistant variants. Already, we have seen variants render vaccines and natural immunity dramatically less effective at preventing COVID in countries like South Africa. With such variants detected in the United States already, we cannot protect Americans from new SARS-CoV2 variants without also immunizing people around the world. Decades of public health research has proven that viruses know no borders. If we do not deal with the pandemic everywhere, we guarantee a resurgence on our own soil.

Furthermore, inequitable vaccine distribution dramatically threatens the global economy. The current systems, structures and approaches to manufacturing and delivering vaccines are costing the global economy trillions of dollars due to the inefficiencies and lack of scale. The United States will shoulder a significant fraction of this burden if we do not act to increase vaccine access in low- and middle-income countries. By spending a relatively small amount up front to ensure universal immunization this year, the United States can avoid losing hundreds of billions of dollars in economic activity while ensuring that its citizens can return to routine economic activity without the concern of emerging variants decimating the population.

Taking the lead on global vaccination efforts will allow the United States to reestablish itself as a global public health leader as it did during the HIV epidemic in the early 2000s. Already, vaccine shortages in LMICs

threaten global stability, and senior European Union officials warn that the situation could undermine peace and security internationally. The previous administration's decision to abandon the U.S. government's traditional role in global public health has left a leadership vacuum that has already helped to fuel social unrest around the world. The Biden Administration can fill that vacuum, strengthening diplomatic relations with other nations and building good-will on the world stage.

Increasing vaccine manufacturing capacity is only the first step of the global vaccine response. Universal immunization requires not only enough vaccine supply, but also a robust, multilateral implementation plan focused on distributing and administering vaccines around the world. Such a plan requires meaningful engagement from all countries, public health experts, relevant NGOs, and private industry. The sooner we maximize our vaccine manufacturing capacity, the sooner an implementation plan can be developed.

By utilizing its unique position as the owner of intellectual property protecting the NIAID/Moderna vaccine plus statutory authorities like the Defense Production Act and 28 U.S.C. § 1498, President Biden's administration can take the bold, decisive action required to tackle the largest public health challenge in a generation. A public production model, executed in partnership with Moderna, can rapidly increase vaccine manufacturing capacity while serving both the federal government's and Moderna's best interests. Such a plan would equip the world with the technology necessary to address emerging vaccine-resistant variants, thereby saving countless lives, supercharging economic recovery, and making the United States the preeminent leader in global public health once more. Without it, **everyone, everywhere** will continue to suffer.



APPENDIX

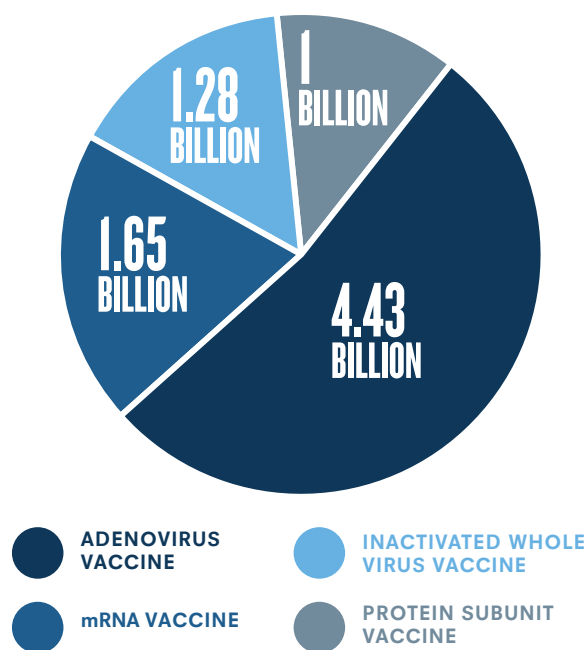
COVID-19 VACCINE TECHNOLOGY LANDSCAPE

Vaccines aim to induce an antibody-based adaptive immune response by exposing and stimulating a specific type of white blood cell known as B-cells. Antibodies are ‘Y’-shaped proteins that recognize and bind to specific regions, known as epitopes, on antigens. Once an antibody binds to an antigen on the pathogen, it either neutralizes the pathogen (for example, an antibody can bind to spike protein on SARS-CoV2, preventing it from infecting human cells) or activates other immunological processes (like the complement cascade) to help defeat the pathogen. The bulk of the world’s planned production capacity for COVID-19 vaccines — more than 50% — centers on those that use adenovirus vectors to elicit an immune response, with the AstraZenca/Oxford vaccine, making up the largest proportion of production capacity. Apart from mRNA vaccines, all vaccines require extensive use of **cell culture** for their manufacture.

Cell culture is the process of growing cells in controlled environments in **growth medium** — a mixture of substances containing nutrients for cell growth, chemicals to maintain an optimal environment for the cells (like salts, and buffers to maintain the correct pH), and other components (like growth factors) crucial for keeping cells alive and growing. We generally distinguish between **microbiological** cell culture — which refers to the growth of single cell microorganisms (like bacteria or yeast) — and **tissue** culture, which refers to the growth of cells from the tissue of a multicellular organism (like a human or a moth). Both research and industrial scale culture rely on **cell lines** — a population of cells derived from a single cell progenitor. For tissue culture, cell lines must be **immortalized** for continuous replication. This is because most cells from healthy multicellular tissue (like a kidney or a liver) will not normally proliferate indefinitely in cell culture conditions. Generally, cell culture at the research scale is generally performed within **cell culture flasks** — specialized vessels generally made of glass or plastic. Industrial scale cell culture is generally done within **bioreactors** — highly

2021 PLANNED PRODUCTION CAPACITY BY VACCINE TYPE

(in coverage by dose amount per person who could be vaccinated)



specialized machines, ranging from single liter to thousands of liters in size, that maintain the highly specialized environment necessary for cell culture.⁶⁰

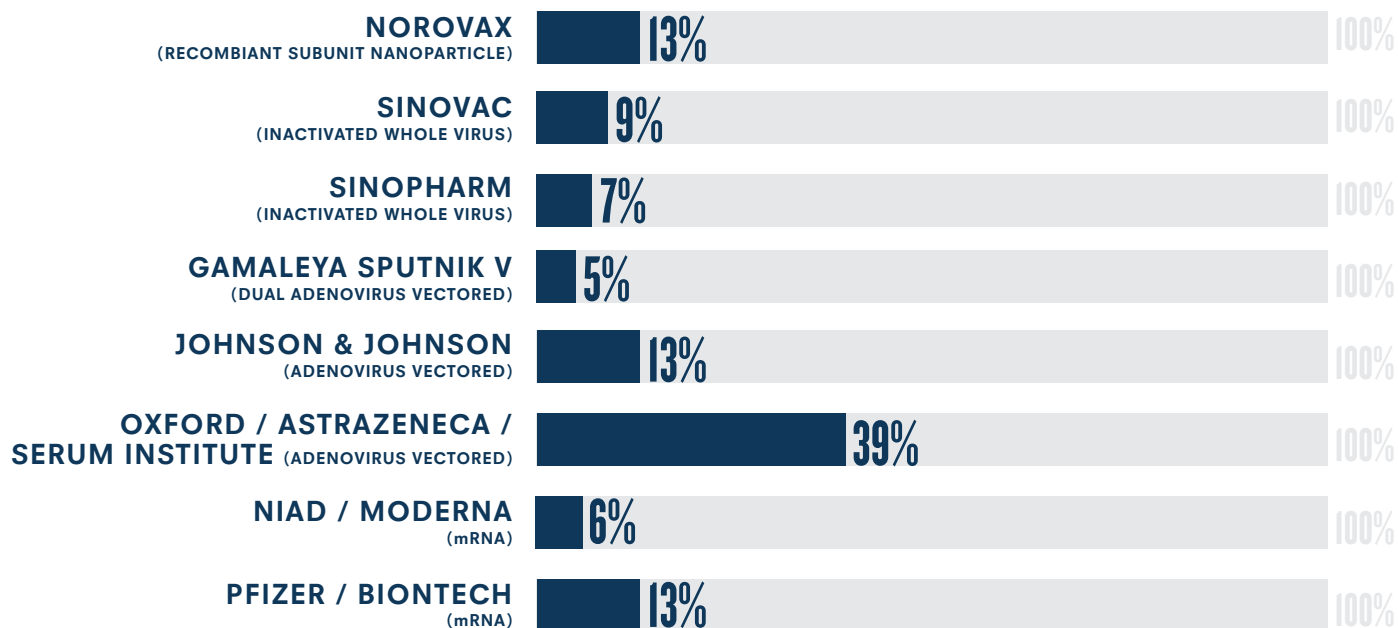
Inactivated whole virus vaccines consist of whole SARS-CoV2 viral particles (known as ‘virions’) produced in cell culture and rendered non-infectious via treatment with special chemicals — a process known as inactivation. (Other inactivated whole virus vaccines include Jonas Salk and colleagues’ polio vaccine and most influenza vaccines.) An inactivated whole virus cannot induce a CD8+ T-cell response, due to its inability to induce expression of viral proteins within the cell.

Manufacturing Process

Manufacturing whole virus vaccine involves generating a large number SARS-CoV2 virions in mammalian cell

ANNOUNCED GLOBAL PRODUCTION COMMITMENTS FOR COVID-19 VACCINES AS A PERCENTAGE OF GLOBAL POPULATION IN 2021

PERCENT OF GLOBAL POPULATION THAT CAN BE COVERED



culture, generally in Vero cell lines, in large bioreactors. This process requires highly specialized biocontainment facilities capable of operating at biosafety level 3.

During the manufacturing process for both COVID-19 vaccines, the number of virions produced varied significantly based on which viral strain was used as seed viral stock. This challenge will likely slow down regulatory approval and adoption for modified versions to combat new variants of SARS-CoV2.

Safety and Efficacy

Two inactivated whole virus vaccines for COVID-19 have released some phase 3 efficacy and safety data – the **BBIBP-CorV** vaccine from China National Pharmaceutical Group Corp, commonly known as Sinopharm, and **CoronaVac** from Sinovac Biotech Ltd. None of the phase 3 data has been peer reviewed, and significant questions remain about what the data indicates.

For **BBIBP-CorV**, Sinopharm has stated that it is 79.34% effective at preventing symptomatic COVID-19 disease, based on interim analysis of phase 3 clinical trials.⁶¹ However, the company has not released details such as the number of events in each trial arm or the definition of the clinical trial end points, thereby making it impossible to objectively evaluate this claim.

Similarly, a lack of transparency from Sinovac and clinical trial investigators has clouded objective

evaluation of **CoronaVac**. Although efficacy was initially reported as above 90% from a small Turkish phase 3 clinical trial, a larger phase 3 study in Brazil showed that vaccine efficacy was only 50.4% effective in preventing severe and mild COVID-19 disease.⁶²

No phase 3 trial results have been reported for either vaccine in countries with partially resistant strains circulating, like South Africa.

Advantages

- Able to utilize existing infrastructure of large-scale bioreactors for production.
- Both vaccines can be stored and distributed at normal refrigerator temperature

Disadvantages

- Unclear efficacy
- Requires biosafety level 3 biocontainment facilities for production of SARS-CoV2 virions and downstream processing until after the inactivation step
- Likely difficult for manufacturing process to produce vaccines that can combat new variants
- Production process depends heavily on large scale mammalian cell culture

PROTEIN SUBUNIT VACCINES

Protein subunit vaccines work by injecting the patient with protein components (or “subunits”) of the pathogen that function as antigens. Other protein subunit vaccines include hepatitis B vaccines and human papilloma virus (HPV) vaccines. The leading protein subunit vaccine, developed by Novavax, uses an engineered version of the Spike protein of SARS-CoV-2 as an antigen.

Manufacturing Process

Most subunit vaccines produce the antigenic protein(s) recombinantly – i.e. the process of bringing genetic material from multiple sources into a single organism (e.g. the transfer of a viral protein gene into a moth cell line “host”). While recombinant protein production can be done in bacterial cell culture, special processes that occur after the protein is initially produced, known as “post translational modification”, often are needed to make a protein properly antigenic. Often, bacterial cells lack the proper intracellular machinery to do the necessary post translational modifications. Thus, recombinant spike protein production for the Novavax vaccine takes place in Sf9 cells – an immortalized cell line derived from the ovarian tissue of the fall armyworm moth, *Spodoptera frugiperda*.

To get the Sf9 cells to make the engineered spike protein, a specialized virus that infects insect cells, called a baculovirus, is engineered to contain the gene for the spike protein. Baculoviruses that have a foreign gene, in this case, a spike protein, inserted into them are called “baculovirus expression vectors”. Following the selection of a baculovirus expression vector that can properly express the spike protein efficiently, a master “seed stock” of that baculovirus expression vector is created.

To produce the spike protein, a healthy population of Sf9 cells is established within a bioreactor. Next, the bioreactor is inoculated with the spike protein containing baculovirus expression vector. Within the bioreactor, the baculovirus expression vectors infect the Sf9 cells, causing the Sf9 cells to produce the spike protein. After a suitable period (around 3 days), the Sf9 cells are harvested from the bioreactor. The cells then are split open (“lysed”) and the spike protein is extracted from the Sf9 cells. Next, a complex series of purification steps are taken to isolate the spike protein from other components. [€63 SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 elicits immunogenicity in baboons and protection in mice | bioRxiv](#)

For Novavax’s vaccine, the recombinantly produced spike protein is allowed to clump together into a nanoparticle structure ([Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice \(nih.gov\)](#)), although the exact process for this remains unclear in the literature.

Safety and Efficacy

Of the protein-based vaccines, only the Novavax inactivated vaccine has released phase 3 efficacy data. Interim phase 3 data from a trial in the United Kingdom (n>15,000), showed 89.3% (95% CI: 75.2 – 95.4) in preventing symptomatic COVID-19– with 6 cases in the Novavax group compared to 62 cases in the placebo group.

In South Africa, preliminary results from a phase 2b trial showed a remarkable reduction in efficacy at only 49.4% (95% CI: 6.1 – 72.8). This reduction was presumably due to the 501Y.V2 viral variant that is spreading in South Africa. Indeed, 92.6% of sequenced cases in the South Africa trial were of the resistant variant.

Advantages

- Able to use existing bioreactor capital infrastructure for recombinant protein production, at normal biosafety conditions (BSL2).
- Highly efficacious against non-escape variants of SARS-CoV-2.
- Good cold chain characteristics (4°C for more than six months).

Disadvantages

- Highly dependent on complex tissue culture processes for manufacturing, complicating generating new versions of the vaccine to combat new virus variants.
- Tissue culture processing requires extensive capital infrastructure for both generation of the protein and subsequent downstream processing.

ADENOVIRUS VECTORED VACCINES

Adenovirus-vectored vaccines work by genetically modifying an adenovirus – a type of common cold virus – to deliver DNA that codes for the vaccine antigen to human cells. To transform adenovirus into an adenovirus vector, portions of the viral genome that allow the virus to replicate are deleted. This produces ‘replication incompetent’ that cannot replicate within

the immunized individual but can still deliver the antigenic gene into the patient being immunized.

Once the adenoviral vector has entered the cell, the DNA coding for the antigen is converted into messenger RNA (mRNA) by the human cell's intracellular machinery — in a process known as **transcription**. This transcribed mRNA is then converted into the antigenic protein by the cell's ribosomes — this process is known as **translation**. This antigen then induces an immune response. By producing the antigenic protein within the cell, adenovirus-vectored vaccines can induce a CD8+ T-cell response, as well as a CD4+ T-cell response and a B-cell response.

Because an adenovirus-vectored vaccine is derived from an infectious virus, it is possible that people will have existing immunity to the adenovirus vector. For example, if an individual had a common cold due to infection with a certain adenovirus, it is likely that such an individual would have immunity to a vaccine vector derived from the same adenovirus. This 'anti-vector immunity' can reduce the ability of the adenovirus vector to deliver the antigenic DNA to cells and reduce the ability of the vaccine to provoke a strong immune response. Thus, the selection of a proper adenovirus vector — one where people do not have large levels of pre-existing immunity to the vector, is crucial for the development of a successful vaccine.

People immunized with an adenovirus-vectored vaccine develop an immune response not only to the antigen the vector codes for, but also to the vector itself. Generally, the immune response is much weaker to the vector than to the antigen it codes for. However, this 'post immunization anti-vector immunity' may reduce the efficacy of subsequent booster shots. Certain adenovirus-vectored vaccines, like the Sputnik V vaccine, uses two different adenovirus vectors for the first and second shot — an approach known as a "heterologous prime boost" strategy — to prevent the post immunization anti-vector immunity from the first dose reducing the efficacy of the second vaccine.

Prior to COVID-19, no existing adenovirus-vectored vaccine had been widely used outside of the research context in humans. Critical safety concerns exist for this type of vaccine. For example, the use of adenoviral vector 5 (Ad5) — used in the Sputnik V vaccine — is associated with an increased risk of HIV infection in multiple clinical trials.

Manufacturing Process

The manufacturing process for adenoviral vector vaccines is extremely complex. Highly experienced manufacturers — like Johnson and Johnson⁶⁵ and

AstraZeneca⁶⁶ — have struggled with the scale up of their adenoviral vector vaccine candidates. The production of adenovirus vectors takes place in large scale tissue culture operations, utilizing bioreactors.

The basic problem of replication incompetent adenovirus vector production is simple to grasp: how do you reproduce something that is, by design, replication incompetent? As discussed above, adenovirus vectors have critical genes necessary for replication deleted. To produce adenovirus vectors in the factory, specialized engineered immortalized human cell lines (generally HEK293 or PER.C6 cells) are made that have the deleted **adenovirus genes** inserted into the cell line's genome. This allows the adenovirus vector to multiply within the **engineered cell line**, but nowhere else.

In order to produce the adenovirus vector, the genome of adenovirus vector vaccine is prepared within a host system, such as the bacteria *E. coli* (e.g. bacterial artificial chromosome), that allows easy genetic manipulation. Once the gene or genes that encode the desired antigen is properly inserted into the adenovirus vector genome, the adenovirus vector genomic DNA is purified from its bacterial host and linearized. The linearized genome is next transfected (i.e., the process of delivering purified DNA directly into cells in the laboratory) into the engineered cell line. Following transfection, the engineered cell line produces replication incompetent viral vectors.⁶⁷

These initially produced adenovirus vectors are individually separated in a process known as **plaque purification** and characterized for their suitability for commercial production. Once a vector is selected, a **master viral vector seed stock** is created, which all further production runs for the vaccine will be based on. For production, the master viral vector seed stock is replicated in small batches into a **working viral vector seed stock**.⁶⁸

Like the viral vector, the engineered cell line used for production must also be validated and a **master cell bank** created. For production, the master cell bank is replicated in small batches into a **working cell bank**. A bioreactor is inoculated with cells from the working cell banks. Once the cells have reached the appropriate density within the bioreactor, the bioreactor is infected with viral vectors from the working viral vector seed stock. After a suitable period, cells containing the adenoviral vector are lysed open and harvested. The production of adenoviral vectors is highly dependent on achieving a high cell density within the bioreactor, which in turn, impacts vector yield, and overall productivity of the production process. Adenoviral vectored vaccines generally require large doses — on

the order of 10 billion to 100 billion vectors per dose.

After harvest, a complex series of steps are taken to purify the adenovirus from cellular and other containments.

Caution must be taken to prevent accidental production of replication competent adenovirus during vector production. The inserted adenovirus genes in the engineered cell lines may combine with the adenovirus vector genome, rendering the vector replication competent. This process, known as **recombination**, is of special concern when adenovirus type 5 (Ad5) based vectors are produced in HEK293 cells, as they are for the boost dose of Sputnik V.

The extreme complexity of the manufacturing process for adenoviral vectors poses not only a challenge for initial production, but also for any subsequent modification necessary to combat new variants. Any new variant will require re-engineering the initial vector design, requiring selection and generation of new master and working viral vector seed banks, as well as subsequent process optimization, a lengthy and complex process. Furthermore, the likely need to switch adenovirus vector types completely to induce immunity for new variants in previously vaccinated individuals not only complicates production, it also will require new clinical trials to show that the new vector is safe, immunogenic, and effective.

Safety and Efficacy

Three adenovirus-vectored vaccines have released phase 3 efficacy data:

The **AstraZeneca/Oxford Vaccine, AZD1222**, uses a replication incompetent simian adenovirus (ChAd) serotype Y25 (ChAdOx1) vector and is also being produced under license by Serum Institute. It showed a **70.4% efficacy (95% CI: 41.0 – 75.7)** in preventing symptomatic COVID-19⁶⁹ following two doses of the vaccine. Concerningly, recently released data from South Africa showed an extraordinarily low efficacy (below 25%) in the vaccine preventing COVID-19 disease, presumably due to the variant spreading there. This low efficacy caused South African officials to suspend planned use of the vaccine.⁷⁰ AZD1222 uses an unmodified full-length SARS-CoV2 spike protein as its antigen.

The **Johnson and Johnson vaccine, JNJ-78436735**, using a replication incompetent adenovirus type 26 (Ad26) vector, **showed efficacy of 72%** in preventing moderate to severe COVID-19 in the United States, 66% in Latin America and 57% in South Africa, after a **single dose**.⁷¹ These results have not been peer-reviewed

and confidence intervals have not been provided. JNJ-78436735 uses a pre-fusion conformation stabilized full-length SARS-CoV2 spike protein as its antigen, like the Moderna/NIAID, Novavax, and Pfizer vaccines.

The **Gamaleya Research Institute of Epidemiology and Microbiology's vaccine, Sputnik V**, utilizes two distinct replication incompetent adenovirus vectors, adenovirus type 26 (Ad26) as the first or 'prime' dose, and adenovirus type 5 (Ad5) as the second or 'boost dose' — a 'heterologous prime boost' approach. This vaccine was **91.6% (95% CI 85.6–95.2)** effective in preventing symptomatic COVID-19 disease.⁷² No data is available from countries, like South Africa, with vaccine-resistant strains circulating. The use of adenovirus type 5 (Ad5) boost vector is extremely concerning, given the association of that vector, in multiple clinical trials, with increased rates of HIV infection.⁷³ Unfortunately, none of the clinical trials evaluating Sputnik V have reported safety data on HIV risk.

Advantages

- Good temperature characteristics (all leading candidates can be stored for at least three months at 2-8°C).
- At least one adenovirus-vectored vaccine, made by Johnson and Johnson, was effective as a single dose.
- Can utilize existing bioreactor manufacturing capacity,

Disadvantages

- Extremely complex manufacturing process that likely will pose a significant barrier to production of both initial and new variant booster products.
- Extremely high dose (10^{10} to 10^{11} vector particles per shot) required, further complicating manufacturing .
- Unlikely to be able to use the same vector for new variant boosters in previously immunized individuals, due to anti-vector immunity.
- Safety risks with certain adenoviral vectors, like Ad5.

mRNA VACCINES

mRNA vaccines work by inserting messenger RNA (mRNA) that codes for the antigen of interest directly into the cells of individuals who have been injected with the vaccine. The production process

for mRNA vaccines is far simpler than other vaccine technologies. Thus, these vaccines can be rapidly developed for emerging pathogens and rapidly adapted to new strains of a pathogen that may be resistant to older vaccines.

Although conceptually simple, the hard part of making mRNA vaccines work is twofold. First, it is difficult getting the mRNA *into* cells. To address this problem, leading mRNA vaccines for COVID-19 have their mRNA “payload” encased in a “lipid nanoparticle” (LNP), which allows the LNP to fuse with the cell membrane and the mRNA to enter the cell.

Second, once inside the cell, barriers arise that can prevent the mRNA molecule from being translated into protein before the mRNA molecule is degraded by intracellular processes. The introduction of foreign RNA from a mRNA vaccine appears like an infection with an RNA virus and can trigger specialized antiviral sensors, known as **patten recognition receptors** (PRRs), like Toll-like Receptors (TLRs) 7 and 9, that reduce the cell’s ability to translate mRNA into protein. To prevent this, chemical modifications are made to certain constituent components of the RNA molecule to reduce detection by the PRRs. Thus, the mRNA in leading COVID-19 vaccines is **modified** mRNA or “modRNA”, which allows efficient translation of the antigenic protein while resisting the host cell’s antiviral defense system.

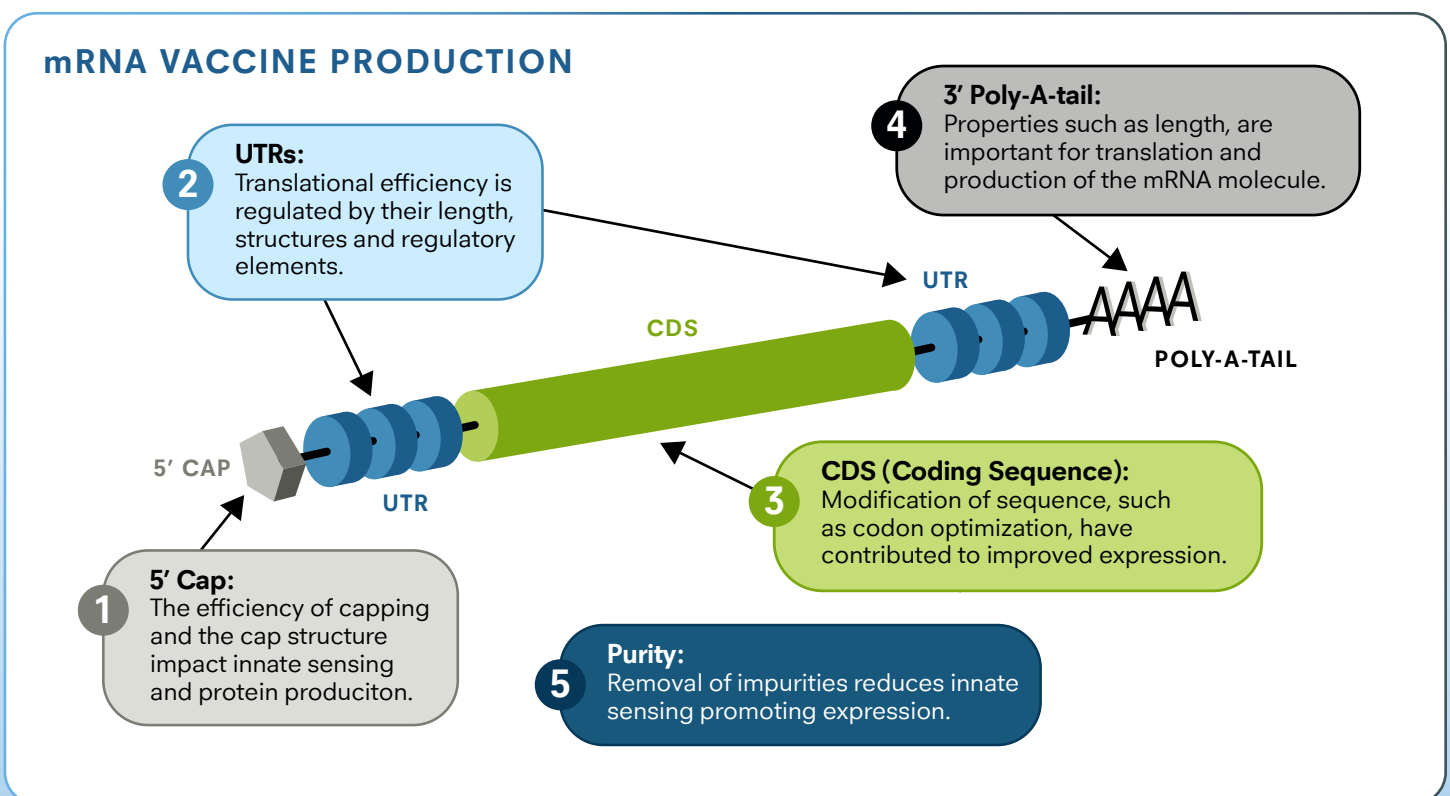
Prior to COVID-19, no mRNA vaccines had been used outside of research context. Thus, before 2020, no industrial capacity existed to produce mRNA vaccines

at scale. Despite this, the production process’s inherent advantages enabled rapid capacity scale up – allowing global manufacturing capacity to reach multi-billion doses per year in less than a year.

Manufacturing Process

The mRNA vaccine production process is distinct from other vaccine technologies in that the production process is almost entirely **cell free** – meaning that production is not dependent on cell culture-based manufacturing processes, but instead on synthetic processes that are far more flexible in production scale up.

The first step in mRNA vaccine production is DNA **template generation**. The DNA template contains the sequence of the vaccine’s mRNA payload, containing the gene(s) for the antigen, as well as other structural elements, encoded as DNA rather than RNA. This allows production of large quantities of material through standardized processes, like plasmid DNA amplification or **enzymatic** DNA synthesis. Kilogram scale production of plasmid or enzymatically produced DNA is available commercially through numerous providers. Critically, this is the only step in the entire mRNA vaccine production process that is dependent on a cell-based process (and only if plasmid DNA amplification is used). While some have noted that DNA template generation could be a rate limiting factor in production of mRNA vaccine, enzymatic cell free based technology that avoids the use of a bacterial host (like *E. coli*), could allow rapid increases in production.



For example, a single United Kingdom facility will be able to produce 1 kilogram per *month* of linear DNA through an enzymatic synthesis process.⁷⁴ Following production and purification of template DNA, the DNA is linearized (if it is in plasmid form) through treatment with restriction endonucleases.

Following RNA generation and DNase digestion, the modRNA mixture is purified. This both removes unwanted leftover components from the RNA synthesis reaction (like T7 RNA polymerase) and ensures that incomplete or uncapped RNA is removed.

The purified modRNA proceeds to **lipid nanoparticle encapsulation**. This step encases the modRNA in a lipid nanoparticle (LNP). The use of cationic (i.e. positively charged) ionizable lipids enables the formation of an RNA containing LNP. Because RNA is negatively charged, the negatively charged RNA and the positively charged ionizable lipids are attracted to each other through electrostatic forces. This helps the lipid nanoparticle form around the modRNA core.

To form LNPs, the modRNA (dissolved in a water-based solvent) is mixed with a solution containing the lipid mixture (dissolved in an amphiphilic solvent, like ethanol). Although exact production details vary from manufacturer and have not been disclosed, large scale production processes used for lipid nanoparticle encapsulation generally can be divided into two general regimes: **macrofluidic mixing** and **microfluidic mixing**. Macrofluidic mixing refers to mixing processes that occur at normal physical scale commonly used in production of biopharmaceuticals. Microfluidic mixing, in other hand, utilize mixing process at the sub-millimeter scale, utilizing specialized fabricated mixers to do this.

Macrofluidic mixing generally uses a variant of classical "T-junction" mixing that allows the flow of two distinct fluid flows (i.e. one containing the RNA containing mixture and one containing the lipid mixture) into a single combined fluid flow. The two fluid flows mix together turbulently, forming nanoparticles. Although some experience with macroscopic T-junction mixing for generation of nucleic acid containing LNPs has been published, it is generally thought to be less suited for generation of LNPs for RNA applications than microfluidic approaches.

Microfluidic mixing enables mixing in fluid paths (i.e tubing) at the sub-millimeter scale. This tiny scale is conducive to the creation of **laminar fluid flow** (i.e. the particle path of the fluid is smooth, with minimal interaction between adjacent layers of fluid). Laminar fluid flow allows a well-defined interface between the RNA containing solution and the lipid containing solution. This allows the device to precisely control the mixing

conditions of the two fluids – allowing exquisite control of key LNP parameters like size. Multiple methods of microfluidic mixing for nanoencapsulation exist.

Following LNP encapsulation, purification, filtration, and concentration occur.

The advantages of the mRNA production process are easy to see. First, with the possible exception for plasmid DNA amplification, the entire process is cell free. This not only allow rapid production scale up, but also allows the process to be rapidly adapted for new antigens, such as those needed for vaccines to combat new variants.

Safety and Efficacy

Two mRNA vaccines have published phase 3 efficacy and safety data. The vaccine from a collaboration between Pfizer and BioNTech, known as **tozinameran**, **showed 95% efficacy (95% CI:90.3 – 97.6) in preventing symptomatic COVID-19 in a large phase 3 randomized control trial after two doses**. No information is available about the efficacy of the vaccine in countries where resistant variants are circulating. Preliminary evidence supports the ability of the vaccine to reduce transmission on a population, reduce the viral load of infected individuals soon after the first dose of vaccine, and be efficacious after a single dose.

mRNA-1273, a vaccine developed by a collaboration between NIAID and Moderna, **showed a 94.3% efficacy in preventing symptomatic COVID-19**. No information is available about the efficacy of the vaccine in countries where resistant variants are circulating.

Advantages

- Extremely efficacious candidates.
- Extremely rapid manufacturing process – proven to be able to rapidly scale.
- Nearly cell free manufacturing process allows rapid development and production of new vaccines to combat new variants.

Disadvantages

- Cold chain characteristics less than ideal (NIAID\ Moderna's candidate can only stay at 4C for 30 days, otherwise regular freezer temperatures -20C are required).
- Pfizer\BioNTech's candidate requires -70C for storage.
- Limited standby manufacturing capacity, due to novelty of mRNA vaccines.

SUPPLY CHAIN CALCULATION

TEMPLATE DNA

The DNA template contains the sequence of the vaccine's mRNA payload, containing the gene(s) for the antigen, as well as other structural elements, encoded as DNA rather than RNA. No DNA is in the finished vaccine product. Rather it is used as an intermediate product, for the con process of converting DNA to RNA through industrial, cell-free processes is known as in-vitro transcription (IVT). In classical IVT reactions, the template DNA is destroyed at the end of the reaction run, by the addition of deoxyribonuclease (DNAase), leaving only RNA.⁷⁵ New technologies have been developed that enable the preservation of template DNA between IVT reaction runs.⁷⁶ Some have speculated that template DNA production may be a barrier to scale up of mRNA vaccines.⁷⁷

Generally, the amount of RNA produced by an IVT reaction is on the order of 100 to 1000 times (on a mass basis) as much as the template DNA put in – this is known as the **amplification factor**. [manual HiScribe T7 In Vitro Transcription Kit E2030 \(neb.com\)](#) [HighYield T7 mRNA Synthesis Kit \(me1Ψ-UTP\), Kits for mRNA Synthesis – Jena Bioscience](#)

Thus, given that per dose, approximately 100 micrograms of template modRNA needs to be synthesized per dose of mRNA-1273, 16 billion doses of mRNA-1273 would require on the order of 160 kilograms of RNA. Even assuming a low IVT amplification factor of 100x, this would only require on the order of 10 kilograms of input template DNA, well within the commercial *monthly* capacity of existing commercial DNA manufacturers.

Given this, it seems highly unlikely that template DNA will be a rate limiting factor for mRNA vaccine production scale up or that significant expenditures will be required to increase existing commercial manufacturing capacity.

5' CAP ANALOGUE

The 5' (pronounced "5 prime") cap is a molecule at the beginning (or "cap") of each mRNA molecule. While natural mRNA has a 5' cap, synthetic mRNA, like that used in vaccines, often use synthetic versions of the 5' cap, known as a "5' cap analogue". The 5' cap is critical to the stability of the mRNA molecule once inside the cell, and its ability to be converted ("translated") into protein.

For mRNA-1273, a specific synthetic 5' cap analogue, $m_2^{7,3'-O}GP_3(2'OMe)ApG$,⁷⁸ is used. We assume that the average molecular weight of modRNA sequence, **without the modRNA cap**, is approximately 1 megadaltons and the average molecular weight of $m_2^{7,3'-O}GP_3(2'OMe)ApG$ is approximately 1.1597 kilodaltons.⁷⁹ For each RNA molecule, there is a single synthetic 5' cap analogue attached.

Therefore, in each 100 microgram dose of mRNA-1273, we estimate that there is approximately 80 nanograms of the synthetic 5' cap $m_2^{7,3'-O}GP_3(2'OMe)ApG$. This would trivially translate to approximately on the order of 1 kilogram required of $m_2^{7,3'-O}GP_3(2'OMe)ApG$ for 16 billion doses.

However, the process of adding the 5' cap to the modRNA, aptly named "capping", is relatively inefficient. We conservatively assume that capping occurs simultaneously with in-vitro transcription reaction, a process known as co-transcriptional capping.⁸⁰ This requires that the 5' cap analogues be incubated with ribonucleotide triphosphates (rNTPs) in the IVT reaction. Conservatively, if the ratio of rNTP to 5' cap analogue is 4:1⁸¹ in the co-transcriptional capping reaction, and the overall yield of rNTP to finished modRNA is only 10%⁸² we likely increase the need for $m_2^{7,3'-O}GP_3(2'OMe)ApG$ feedstock by an order of magnitude, so on the order of 10 kilograms would be required for 16 billion doses.

While there is no publicly available information on the size or the maturity of the 5' cap analogue supply chain, the nature of the synthesis of 5' cap analogues seem amenable to global production scale up on the order of 10 kilograms.

NI-METHYLPSEUDOURIDINE TRIPHOSPHATE

N1-methylpseudouridine triphosphate [$N1m\Psi(PO_4)_3$] is one of the four ribonucleoside triphosphate (rNTPs) used in the in vitro transcription reaction to generate the modified RNA for mRNA vaccines. Unlike the other 3 rNTPs, $N1m\Psi(PO_4)_3$ is a **modified** ribonucleotide, that is not commonly used in other production processes. In a given 100 microgram dose of mRNA-1273, there is approximately 20 micrograms of $N1m\Psi$, incorporated in mRNA molecules. The amount of $N1m\Psi(PO_4)_3$ for feedstock would be approximately an order of magnitude more than this. Thus, we estimate that the amount of $N1m\Psi(PO_4)_3$ feedstock required is on the order of 1 to 10 metric tons for 16 billion doses. Given the ease of synthesis of this compound, we believe this should not pose a barrier to production scale up.

LIPIDS

Four different lipids are used in the Moderna vaccine: polyethylene glycol 2000 dimyristoyl glycerol (PEG-DMG), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and a proprietary cationic ionizable lipid, “SM-102”, with the total lipid content being 1.93 mg⁸⁵ per dose. SM-102 is the proprietary name for heptadecan-9-yl 8-((2-hydroxyethyl) (8-(nonyloxy)-8-oxooctyl)amino)octanoate, PubChem CID: 13958167. SM-102 is likely the primary lipid, by mass, in the Moderna vaccine. Although, once again, Moderna has not disclosed the lipid ratios for mRNA-1273, we estimated this using Moderna’s previously published molar ratios of the lipids making up their mRNA containing lipid nanoparticles used for other vaccine candidates.⁸⁴

Although 18,080 kg of SM-102 appears to be a lot, publicly disclosed information shows that the supplier of lipids for Moderna, Cordent Pharmaceutical, has already increased their lipid production capacity by over 50 times, to meet demand from Moderna, and can already provide three to four times the maximum amount of lipids required by Moderna current production plans, and is already planning on supplying other mRNA vaccine manufacturers, in addition to providing Moderna.⁸⁶

Furthermore, additional lipid manufacturers are adding capacity in anticipation of additional lipid demand for future mRNA-based therapeutics.⁸⁷ Therefore, it is unlikely that lipid production will be a significant barrier to production scale up, although further investment in infrastructure for lipid production and purification may be necessary.

NANOPRECIPITATION

The process of encapsulating an mRNA payload within a lipid nanoparticle is called “nanoprecipitation”. For mRNA vaccines, this process generally works by precisely mixing the RNA containing mixture (in a water-based solution) and the lipid mixture (in an ethanol-containing solution) to produce lipid nanoparticles (LNPs). The details of the lipid nanoparticle (LNP) generation used in the production of either the NIAID/Moderna vaccine or the BioNTech/Pfizer vaccine have not been disclosed to the public, however, based on publicly available information, it is reasonable to assume that this process uses **microfluidic** mixing, although there is limited evidence that

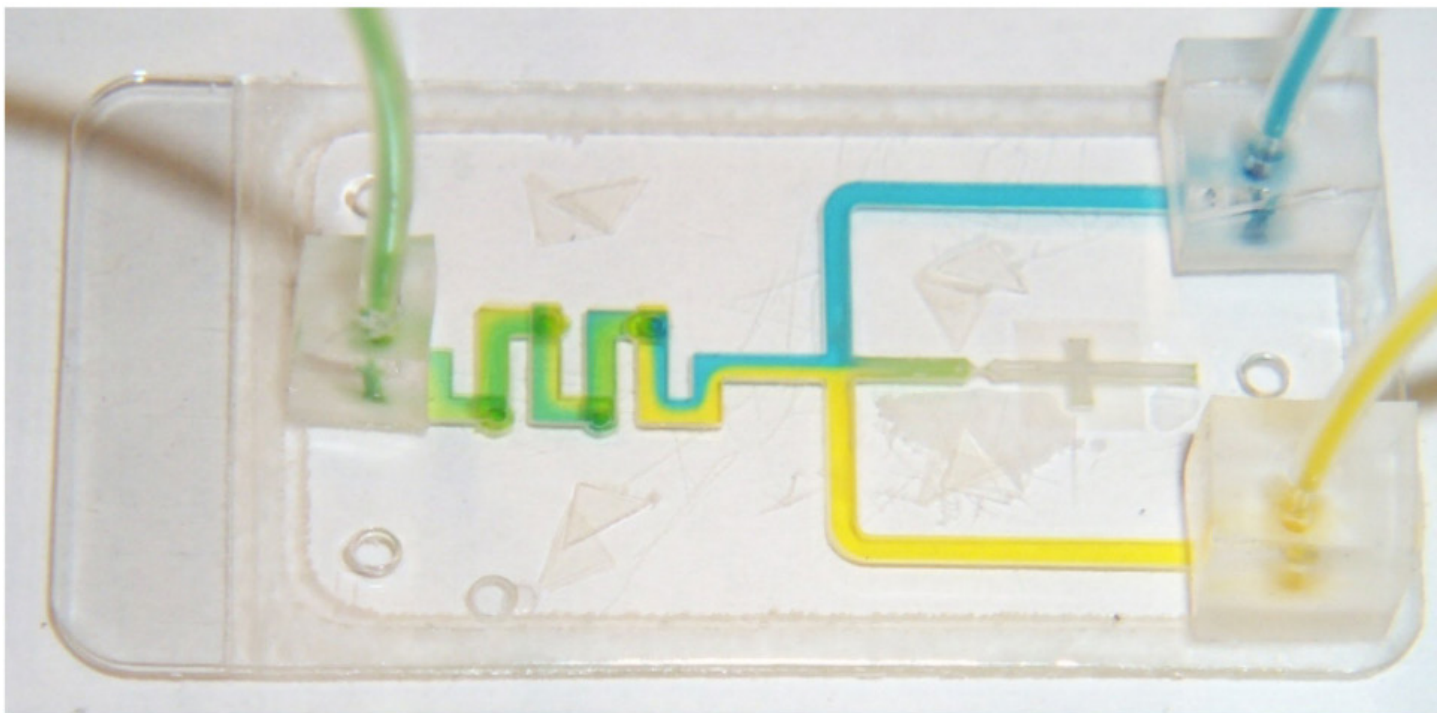
Microfluidic mixing, as its name implies, involves manipulating fluids that are constrained in small — generally less than a millimeter in size — spaces. This allows extremely precise control over mixing dynamics. In particular, this tiny scale is conducive to the creation of **laminar fluid flow** (i.e. the particle path of the fluid is smooth, with minimal interaction between adjacent layers of fluid). Laminar fluid flow allows a well-defined interface between the RNA containing solution and the lipid containing solution.

A common method of generating RNA containing lipid nanoparticles microfluidically utilizes “staggered herringbone” mixers. A microfluidic staggered herringbone mixer consists of a narrow fluid path (between 10 and 100 microns in width) that is interrupted periodically by physical ridges (between 10 and 100 microns in height and width), shaped like herringbones. As the fluid flow encounters the herringbone ridges, the well-defined interface between

CONSTITUENT LIPID PER DOSE OF MRNA-1273, ASSUMING A MOLAR RATIO OF 50:10:38.5:1.5 (SM-102: DSPC: CHOLESTEROL: PEG-DMG)

LIPID	EMPIRICAL FORMULA	MOLAR MASS	ESTIMATED MASS REQUIRED PER DOSE	ESTIMATED MASS REQUIRED FOR 16 BILLION DOSES
SM-102	$C_{45}H_{87}NO_7$	754.17921 g/mol	1.13 mg	18,080 kg
DSPC	$C_{44}H_{88}NO_8P$	790.14958 g/mol	0.24 mg	3,840 kg
Cholesterol	$C_{27}H_{46}O$	386.65606 g/mol	0.45 mg	7,200 kg
DMG-PEG 2000	$C_{122}H_{242}O_{50}$ *	2509.20984 g/mol*	0.11mg	1,760 kg

*PEG-DMG is a polydisperse compound, we assume an average empirical formula of $C_{122}H_{242}O_{50}$ per source.⁸⁵



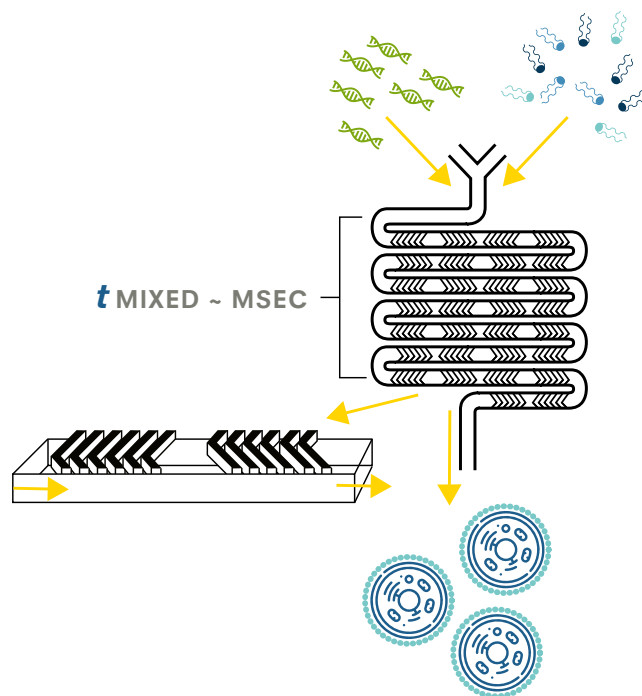
Demonstration of laminar fluid flow in a microfluidic “T-junction” mixer. Note the initially well defined interface between the yellow and blue fluids – which then carefully mixes to make a green fluid flow.

COURTESY: UNIVERSITY OF WISCONSIN – MADISON.

the RNA- and lipid- containing fluids is interrupted, and two fluid streams mix together rapidly (on the millisecond time scale) in an extremely small mixing volume (on the nanoliter scale), resulting in the generation of RNA containing LNP. This results in a specialized form of mixing known as “chaotic advection”, that allows exquisite control of critical LNP characteristics, like size, as well as ensuring a high encapsulation efficiency.

It has been speculated by some that the need to fabricate these specialized microfluidic mixers may prevent scale up.⁸⁸ While neither Moderna nor Pfizer/BioNTech have disclosed details about their nanoprecipitation process, common techniques for microfluidic device fabrication, including laser fabrication, computer numerical control (CNC) micromachining, photolithography, and soft lithography, are extremely amenable to production scale up. In fact, there is extensive available commercial microfluidic fabrication capacity within the United States, which can produce thousands per month of custom designed microfluidic mixers with less than a month-long turnaround time.

MICROFLUIDIC STAGGERED HERRINGBONE MIXING



FILL AND FINISH

The last step of the vaccine production process is known as “fill and finish” and involves the final steps of filling vials with finished vaccine drug substance, capping, freezing (if necessary), labeling the vials, and preparing them for shipment. Existing pharmaceutical capacity is unlikely to be able to deal with fill and finish capacity necessary for supplying global vaccination needs. Increasing the capacity of fill and finish globally is imperative not only for scale up of mRNA vaccines but scale up of production of any vaccine candidate. Although comparatively simple, production of vaccine drug substance does not matter unless it can be filled, finished, and distributed to the patient.

Fill and finish is something that any vaccination scales up program would be wise to leverage existing and international capacity for. First of all, three out of the historical four largest vaccine manufacturers (GlaxoSmithKline, Sanofi and Merck) – who represent more than 90% of global vaccine revenue – are not producing any COVID-19 vaccines. This represents ample fill and finish capacity that could be repurposed for mRNA vaccines.

Furthermore, ample fill and finish capacity exists internationally. Already, companies like Johnson & Johnson are using local companies to provide fill & finish manufacturing services for their vaccines in South Africa.

Regardless, critical material shortages (like glass vials and stoppers) will likely pose a barrier to scale up for production. While the federal government should work to increase production of these goods – and explore the potential application of fill and finish technology that could rapidly bypass these tech barriers, like plastic based multidose containers, that can dispense 200 or 400 vaccine dose from a single plastic container. The use of such a system can rapidly alleviate the fill and finish rate limiting barrier.

Indeed, two such machines, designed to fill a 400-vaccine dose plastic based multidose contained, could fill more than sixteen billion doses in a single year.



ENDNOTES

INTRODUCTION

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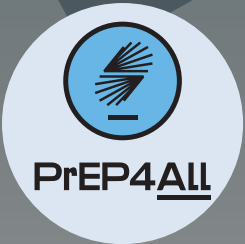
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