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Novavax

— An *Overview* —

By Omar Guzman

Photo illustration by Pavlo Gonchar/SOPA Images/LightRocket via Getty Images

— Current Vaccine Rollout —

149 countries have started vaccinating against COVID-19. In the United States, 29.3% of the population has received at least one dose, while 16.3% has been fully vaccinated.[1] This puts the **US** behind only **Israel**, the **United Kingdom**, **Chile**, and **Bahrain** in terms of percent of population given at least one dose of vaccine, from highest to lowest, in that order.

So far, there are three vaccines that have been authorized by the U.S. Food and Drug Administration[2]:

1. **Pfizer-BioNTech**	Date Granted emergency use authorization:	**12/11/20**
2. **Moderna**		**12/18/20**
3. **Johnson & Johnson**		**2/27/21**

(*From Yale Medicine: Comparing the COVID-19 Vaccines: How Are They Different?*)

The first two (**Pfizer** and **Moderna**) work similarly, using new messenger RNA-based technology where the vaccine ***delivers a tiny piece of genetic code from the SARS-CoV-2 virus to host cells in the body that functions as instructions to make copies of the infamous coronavirus spike proteins***. These proteins stimulate an immune response, producing antibodies and developing memory cells that will recognize and respond if the body is infected with the actual virus.

Pfizer has proven 95% effective against the original strain, while Moderna's is 94.1%. They each require two doses—Pfizer's are three weeks apart while Moderna's are four. The former requires ultra-cold temperature-controlled units (-94° Fahrenheit) while the latter requires only standard freezer temperatures, and can be stored for up to 30 days using normal refrigeration, making it easier to distribute and store.

Johnson & Johnson's vaccine works a bit differently. It is a **carrier**, or virus vector, vaccine, and is easier to store and requires only one shot. Scientists **engineer a harmless adenovirus** (a common virus that, when not inactivated, can cause colds, bronchitis, and other illnesses) **as a shell** to **carry genetic code on the spike proteins to the cells** (similar to a Trojan horse). The shell and the code can't make you sick, but once the code is inside the cells, the cells produce a spike protein to train the body's immune system, which creates antibodies and memory cells to protect against an actual SARS-CoV-2 infection. It has shown 72% overall efficacy in the US.

[1] https://graphics.reuters.com/world-coronavirus-tracker-and-maps/vaccination-rollout-and-access/
[2] https://www.yalemedicine.org/news/covid-19-vaccine-comparison

Supplies

As of January 21, 2021, **Pfizer** and **Moderna** each promised to provide the United States with 100 million vaccine doses by the end of March, or **enough for 100 million to get the necessary two shots**,[3] which is about 30% of the total population, or 38% of all ~260 million adults (vaccines have not yet been approved for children, but it is likely they eventually will be). It is literally the end of March as I write this, and when comparing against Reuters' data, we're less than a percentage point below Pfizer and Moderna's initial target. Combined, the two companies are manufacturing at full capacity, releasing between 12 to 18 million doses each week, or enough for 6 to 9 million people each week.

More Help is on the Way

Johnson & Johnson pledged **100 million** of its one-dose vaccines to be made available by the end of June, bringing the balance of outstanding individuals still needing a vaccine to about **130 million**.

AstraZeneca has made an arrangement with the US government to provide **300 million doses**, while **Novavax** has agreed to provide **110 million**. **Pfizer** and **Moderna** have been expanding their capacity and hope to provide an additional **100 million doses** by the second quarter of this year. **AstraZeneca's** vaccine has run into trouble recently, as some countries have temporarily suspended use of the vaccine after a number of recipients reported developing blood clots, however the **European Medicines Agency** (**EMA**) stated there is no indication that vaccination has caused these conditions. It is not yet available in the United States, but has requested EUA (emergency use authorization) from the FDA and is awaiting approval.

That brings us to...

[3] https://www.nytimes.com/2021/01/21/health/covid-vaccine-supply-biden.html

— Novavax // NVX-CoV2373 —

The way Novavax' vaccine works is different even from the ones previously mentioned and approved for use in the United States. **NVX-CoV2373** (the formal name for their vaccine) is a protein-based subunit vaccine candidate engineered from the genetic sequence of SARS-CoV-2. The vaccine was created using Novavax' **recombinant nanoparticle technology** to generate antigens derived from the coronavirus spike (S) protein. It is **adjuvanted**[4] with Novavax' patented **saponin-based Matrix-M™** which enhances the immune response and stimulates high levels of neutralizing antibodies. This vaccine candidate does require two doses, spaced three weeks apart.

NVX-CoV2373 contains **purified protein antigen** and can neither *replicate*, *nor cause COVID-19*. In preclinical studies, NVX-CoV2373 induced **antibodies** that **block binding of spike protein to cellular receptors** and **provided protection from infection and disease**. NVX-CoV2373 was generally ***well-tolerated*** and ***elicited robust antibody responses numerically superior to that seen in human convalescent sera*** in **Phase 1/2 clinical testing**.

Novavax' vaccine is currently being evaluated in two pivotal Phase 3 trials: one in the UK that completed enrollment of 15,000 participants aged 18 to 84 in November and another in the US and Mexico (**PREVENT-19**) that began in December. The former trial demonstrated **96% efficacy** against the original strain while the latter enrolled more than **30,000 participants** aged 18 years or older and is being conducted with support from **Operation Warp Speed** (**OWS**), as part of an agreement that includes **$1.7 billion** in funding. In addition, the **Coalition for Epidemic Preparedness Innovations** (**CEPI**) invested **$384 million** to support research on the vaccine. Earlier in March, Novavax CEO Stanley Erck said he believed their vaccine would receive authorization from UK health regulators in April followed by the FDA "a month after" (in May). Its results showed only 49% efficacy against the South African variant but the company has said it has since begun clinical development specifically targeting this new strain.

[4]An **adjuvant** is a pharmacological or immunological agent that improves the immune response of a vaccine.

First- and Second-Generation Vaccines

*From **XIIID Research***

COVID-19 **first-Generation** vaccines (Pfizer and Moderna) are designed for speed, aiming to reduce the severity of the disease as quickly as possible but it is not yet known if they will reduce virus transmission or provide longer-term protection. They target the "spike" protein in SARS-CoV-2 but the protection may not be durable because the presence of antibodies is relatively short-term.

A focus on T cells, specifically "memory CD8+ T cells," may prove to offer more long-lasting protection.

Second-generation vaccines, of which Novavax is one, are identified based on their potential to provide protection with a single dose, exhibit stability in greater temperature ranges, remain stable throughout the manufacturing process, yield an improved or differentiated immune response, and use a diverse range of antigens. They are **historically cheaper** and have had higher levels of **efficacy** and **safety**. An example:

- The FDA approved a second-generation nonavalent HPV (Human Papillomavirus) vaccine a decade after the first was developed. It protected against an additional five high-risk HPV variants not covered by existing vaccines. It demonstrated high immunogenicity with the potential to avoid an additional 18.3 to 20% of cervical cancers.

These types of vaccines have a long and successful track record against numerous pathogens, including influenza, hepatitis B, pneumonia and meningitis. "**Protein subunit**" compounds are **primarily considered second-generation vaccines** and are **among the safest and most effective**. **Subunit vaccines** work by presenting a **targeted antigen** to the **immune system**, **without viral particles**, by using a **specific**, **isolated protein** of the **pathogen**.

A major advantage of protein subunit vaccines is the reduction of adverse reactions, since the actual viral components are not available in it. Additionally, subunit vaccine designs can vaccinate against multiple epitopes (i.e., the part of an antigen to which an antibody attaches itself) from different kinds of pathogens and strains.

Novavax' Technology

*From the **2020 Form 10-K***

Recombinant Nanoparticle Vaccine Technology

Novavax' recombinant nanoparticle vaccines combine the **power** and **speed** of **genetic engineering** to **efficiently produce a new class of highly immunogenic vaccines** that **target a variety of viral pathogens**.

Once a pathogenic threat has been **identified**, the genetic sequence encoding the antigen is **selected** for **subsequent use in developing the vaccine construct**. The genetic sequence may be optimized to enhance protein stability or confer resistance to degradation. **This genetic construct is inserted into the baculovirus Spodoptera frugiperda (Sf9/BV) insect cell-expression system, which enables efficient, large-scale expression of the optimized protein** (cloning). The Sf9/BV system produces proteins that are properly folded and modified – which can be critical for functional, protective immunity – as the **vaccine antigen**. Protein antigens are purified and organized around a **polysorbate-based nanoparticle core**, in a configuration that resembles their native presentation. **This presentation results in a highly immunogenic nanoparticle that is ready to be formulated with Matrix-M adjuvant**.

Our recombinant protein nanoparticle vaccine technology is based on self-assembly of surface protein antigens from pathogenic organisms including viruses, bacteria or parasites. The conformations of these nanoparticles **are similar but not identical to the natural structure of surface antigens of disease organisms, and lack the genetic material required for replication and therefore are not infectious**. Potential immunological advantages of protein nanoparticles may be associated with the nanoparticle conformation and the presentation of key functional **epitopes** that are often immunologically hidden in the native pathogen. This leads to efficient recognition by the immune system's antigen presenting cells that trigger robust immune responses. **Recognition** of the nanoparticle vaccine's repeating protein patterns by the antigen presenting cells' toll-like receptors to stimulate innate immunity and the high purity and lack of synthetic material **adds to the potential safety of recombinant nanoparticle vaccines**. Protein nanoparticle vaccine technology has **expanded our early-stage vaccines in development to include both virus and non-virus disease targets**. Our most advanced protein nanoparticle vaccine candidate is our RSV F Vaccine, which self-assembles from our highly purified F-protein antigen.

Matrix-M Adjuvant

Matrix-M is composed of 40-nanometer particles derived from saponin extracted from the bark of the *Quillaja saponaria Molina tree*. Once purified these particles are fused with a unique formulation of cholesterol and phospholipid. This proprietary adjuvant has demonstrated potent and well-tolerated efficacy by **stimulating the entry of antigen-presenting cells** (**APCs**) into the injection site and **enhancing antigen presentation in local lymph nodes**, which in turn **activates T cell**, **B cell**, and **APC populations**, thereby **boosting immune response**. Matrix-M has been shown to increase neutralizing antibodies and **induces long-lasting memory B cells, which enhances B-cell immunity and recruits and increases the frequency of CD4+ and CD8+ T cells to enhance T cell immunity**. The potent immune-stimulating mechanism of action is designed

to enable a lower dose of antigen required to achieve the desired immune response, ultimately contributing to increased supply and manufacturing capacity. These immune-boosting and dose-sparing capabilities contribute to the adjuvant's highly unique profile.

To date, we have formulated many of the vaccine candidates in our pipeline with Matrix-M, including NVX-COV2373 and NanoFlu. Matrix-M has been well-tolerated in human studies to date.

Adjuvants are predominantly used to enable a vaccine to increase the amplitude of the immune response and qualitatively change it, broadening the immune system's attack against microorganisms and allowing for effective immunization with much lower doses of antigen. Novavax AB has developed a number of adjuvant formulations, all based on our proprietary Matrix technology. These adjuvant formulations possess excellent immunostimulatory features with the ability to increase and prolong the protective benefits of vaccines.

While adjuvants based on novel, poorly characterized substances have been hampered by safety concerns and limited efficacy, Matrix adjuvants stimulate strong antibody and cell-mediated immune responses. Matrix adjuvants may allow for lower antigen doses, **longer-duration immune responses** and carry a lower risk for allergic reactions or other adverse events. Our Matrix technology typically induces strong **cellular activation** of both **Th1** and **Th2** types, thereby generating all classes and subclasses of **antibodies**, as well as **potent cellular responses**, including **cytotoxic T lymphocytes**. Our Matrix-M adjuvant provides a potent adjuvant effect that has been well-tolerated in clinical trials. We also believe that the strong immune response and opportunity to reduce the quantity of antigen dose can significantly reduce the production cost of our vaccines. This means that our Matrix-M adjuvant has the potential to be of significant value when there is inadequate vaccine manufacturing capacity during an emerging disease threat such as an influenza pandemic.

Novavax' recombinant nanoparticle technology works essentially by creating copies of a pathogen's antigens (the spike proteins in the case of COVID-19) and assembling them into nanoparticles at a large scale that don't actually harm the body, but prepare and fortify its defenses (i.e., the immune system). It ultimately works like other vaccines but the underlying technology is different, and potentially more effective and durable than traditional vaccines.

It would be like if you knew someone was planning to commit larceny at a local convenience store, you'd send local law enforcement as well as the store's owner, security and employees, a high-resolution photo of exactly what the suspect looks like so that they'd be prepared for when they finally showed up. If you hadn't tipped them off, the suspect's crime would likely unfold successfully, but now with that suspect's photo in hand, it is highly unlikely they'd even be able to set foot in the store.

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A vaccine works similarly—without it, the pathogen would be able to enter the body undetected since the immune system is unfamiliar with it, like with a **novel** coronavirus. With a vaccine, the immune system will already have developed defenses—antibodies—that are able to block the spike proteins from binding to the body's cells, thus neutralizing the virus' threat.

Novavax — The ***Business***

Ticker: **NVAX**
Name: **Novavax**
Price: **$185.82** (*as of April 1, 2021*)
Number of Shares Outstanding: **73.86 million** (*as of December 31, 2020*)
Market Capitalization: **$13.724 billion**

Price History

March 1, 2021	$240.29	
March 2, 2021	$205.99	
March 3, 2021	$183.61	
March 4, 2021	$158.10	
March 5, 2021	$174.84	
March 8, 2021	$157.87	
March 9, 2021	$169.90	
March 10, 2021	$172.50	
March 11, 2021	$187.63	
March 12, 2021	$202.77	
March 15, 2021	$217.46	
March 16, 2021	$222.23	
March 17, 2021	$225.46	
March 18, 2021	$217.26	
March 19, 2021	$228.25	
March 22, 2021	$237.20	
March 23, 2021	$219.84	
March 24, 2021	$200.24	
March 25, 2021	$178.23	
March 26, 2021	$182.12	
March 29, 2021	$173.75	
March 30, 2021	$173.32	
March 31, 2021	$181.31	
April 1, 2021	**$185.82**	**Now we are in real time**

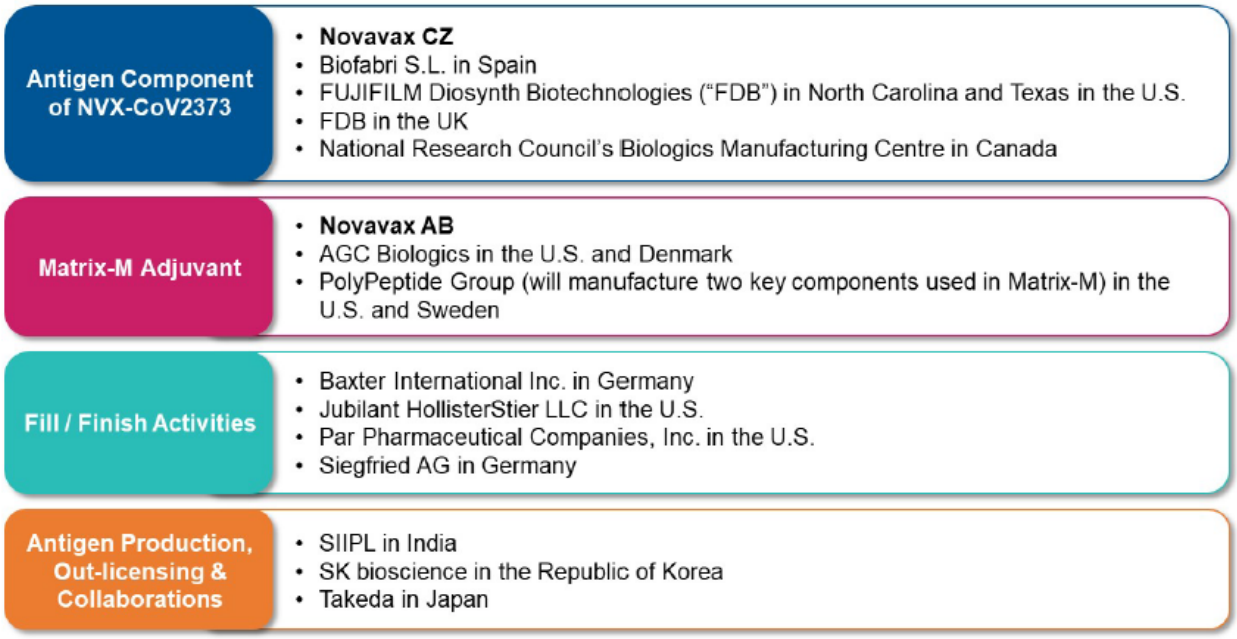
Novavax, Inc., located at 21 Firstfield Road, Gaithersburg, Maryland, was incorporated in 1987. Their product pipeline includes the following therapy areas currently in Phase 3 trials:

- Coronavirus — NVX-CoV2373
- Seasonal Influenza — NanoFlu
- Respiratory Syncytial Virus (RSV) — ResVax

Novavax is currently developing combination vaccines that tackle two or more of these areas, including: **NanoFlu / NVX-CoV2373; NanoFlu / RSV;** and **NanoFlu / NVX-CoV2373 / RSV**

NVX-CoV2373 Manufacturing and Supply

To date, Novavax has **increased its projected global manufacturing production rate** of **NVX-CoV2373** to be over **two billion annualized doses when they're at full capacity**, which is expected to occur in mid-2021. Of this anticipated capacity, **approximately one billion doses** will be manufactured by the **Serum Institute of India Private Limited** (**SIIPL**). Novavax has developed partnerships with entities across the globe to increase its manufacturing capacity and vaccine supplies, including:



NVX-CoV2373 Supply Agreements

Novavax has entered into advanced purchase agreements with various countries globally that, if the vaccine is approved, are expected to result in the delivery of approximately 200 million doses of NVX-CoV2373 throughout 2021 and into the first half of 2022:

Country	Committed Doses & Additional Detail
UK	**60 million** *Option to purchase additional orders from time to time*
Canada	**52 million** *Option to purchase up to an additional 24 million doses*
Australia	**51 million** *Option to purchase up to an additional 10 million doses*
New Zealand	**~11 million**
Switzerland	**6 million**
Summary	**~180 Million Doses**

From what I've learned about Novavax, they seem to be well-positioned to give COVID-19 the knockout punch. Their underlying recombinant nanoparticle technology has the ability to accurately target viral pathogens and create protein antigens organized around a polysorbate-based nanoparticle core, the assembly of which resembles the native presentation of the pathogen being targeted. This process creates highly-immunogenic, long-lasting, yet safe, vaccines that can tackle not only COVID-19 and its variant strains, but also a wide variety of other disease organisms. One of Novavax' near-term clinical development work is evaluating the viability of certain combination vaccines, which, if successful, could potentially lead to a seasonal 3-in-1 or 2-in-1 vaccine shot that would take care of influenza, COVID-19, and RSV.

They are currently seeking approval from the UK Medicines and Healthcare products Regulatory Agency (**MHRA**) and hope to use data from their UK trial for their FDA submission for Emergency Use Authorization (**EUA**), which is expected early in Q2 of 2021. I'm closely watching this stock as well as patiently awaiting the approval of their vaccine for use in the US, as its demonstrated efficacy and lack of adverse side effects and potential for long-term protection have definitely piqued my interest.