COVID-19 Vaccines

by: Richard Jefferys, Treatment Action Group

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Introduction

The development of an effective vaccine against SARS-CoV-2 is an urgent priority. Scientists and doctors began designing vaccines and initiating clinical trials almost immediately after the COVID-19 crisis began. The effort has benefited greatly from the latest microbiological tools, which allowed rapid sequencing of the SARS-CoV-2 genome. Evidence suggests the virus's spike protein is a key target for the immune system, and the gene sequence encoding the protein was quickly available to vaccine manufacturers (the SARS-CoV-2 genome sequence was shared publicly by researchers in China on January 10, 2020).

Multiple initiatives are underway with hopes of dramatically compressing the normal vaccine development timeline and making a product available within a year or less; whether this will prove possible remains to be seen.

Entering the month of September 2020, there are eight different COVID-19 vaccine candidates being tested for efficacy in large trials taking place around the globe. It's unclear when the first results may become available, but it could be in the coming months. Authoritarian regimes in Russia and China have already granted emergency use authorizations to candidates developed in those countries, while aspiring authoritarian despot Donald Trump is reported to be considering a similar step in the U.S.

The COVID-19 vaccine pipeline is evolving rapidly and because it's not possible to update this article with every news item, we recommend the online trackers available from the World Health Organization (WHO), the *New York Times*, BioRender and *Regulatory Focus*.

Prospects for Immunity Against SARS-CoV-2

The extent to which vaccination may be able to induce protective immunity against SARS-CoV-2 is a critical unanswered question. Most experts suggest that virus-induced immune

responses will offer a degree of protection against reinfection or symptomatic disease for at least some period of time (a few months or years), but the WHO has emphasized that there is a lack of definitive, direct evidence to support this view.

Antibodies are Y-shaped proteins made by white blood cells called B-cells in response to an infection. These molecules (including antibodies called IgG and IgA) are used to target a virus or bacterium for destruction upon reinfection, often leading to protection against that pathogen. A comprehensive review of the literature on antibody responses to coronaviruses suggests that several measures may be possible correlates of immunity including serum (blood) IgG and IgA, mucosal IgA, and neutralizing antibody titers.

Studies of the first SARS-causing coronavirus—SARS-CoV-1—reported the persistence of detectable antibodies for at least two years in most cases, although levels declined over time.

Another type of white blood cell—T cells—are also important for responding to infection. Less is known about T cell responses to coronaviruses, but early studies of SARS-CoV-2 have reported induction of virus-specific CD4 and CD8 T cells. Scientific literature is now accumulating demonstrating robust induction of SARS-CoV-2-specific CD4 and CD8 T cell responses in almost all infected people. T cell responses have also been detected in some exposed but antibody seronegative individuals. The evidence indicates that T cell responses need to be considered in vaccine and immunotherapy development for COVID-19.

The presence of memory T cells capable of responding more rapidly to a second exposure was documented in individuals recovered from SARS-CoV-1, but memory B cells could not be detected in peripheral blood six years post-infection. The disappearance of SARS-CoV-1 from the human population, while a welcome development, precluded any analyses of the effect of virus-specific immune responses on reinfection risk (which might've provided clues about protective immunity against SARS-CoV-2).

There are several lines of evidence that support the possibility of inducing protective immunity against SARS-CoV-2. Studies have identified antibodies capable of neutralizing SARS-CoV-2. Preliminary case reports suggest that the infusion of antibodies from individuals who have recovered from COVID-19 (known as convalescent plasma therapy) may have some therapeutic efficacy, but more rigorous analyses are pending. An unusual investigation into a COVID-19 outbreak on a boat found that three individuals who had detectable antibodies prior to embarking did not become infected with SARS-CoV-2; the association between the presence of antibodies and lack of infection was statistically significant.

In an initial small study, two macaques experimentally infected with SARS-CoV-2 resisted a subsequent rechallenge. A larger experiment involving nine macaques published in the peer-reviewed journal *Science* has since echoed these findings, with the researchers noting "protection was mediated by immunologic control and likely was not sterilizing."

A series of three immunizations with an inactivated SARS-CoV-2 vaccine candidate developed by Sinovac Biotech reportedly induced neutralizing antibodies and reduced disease or protected against infection (depending on vaccine dose) in a macaque study published in *Science*. A vaccine developed by researchers at Oxford University in the U.K. has also shown evidence of protection against disease and decreased viral load after single or double (prime-boost) immunizations in macaques challenged with high dose of SARS-CoV-2. More recently, the research group of Dan Barouch at Harvard has demonstrated robust control of a SARS-CoV-2 challenge in macaques immunized twice with DNA vaccine constructs encoding various forms the virus spike protein. The degree of protection correlated with neutralizing antibody responses (see also Carl Zimmer's coverage in the *New York Times*).

Reasons for Caution

Evidence also exists that points to the need for caution about the prospects for vaccination against SARS-CoV-2. Efforts to develop veterinary vaccines for animal coronaviruses have so far met with mixed success. In a number of experimental settings involving other coronaviruses, a phenomenon of antibody-dependent enhancement (ADE) of disease has been described, in which vaccine-induced antibodies interact with the virus in ways that promote (rather than protect against) tissue damage. Studies of SARS-CoV-1 have reported evidence of ADE in mice, ferrets and macaques; however, there are also data supporting efficacy of SARS-CoV-1 vaccine candidates in macaques. So far, none of the multiple published macaque experiments involving vaccination followed by a SARS-CoV-2 challenge have uncovered any evidence of ADE. Whether there is any potential for ADE in humans is uncertain, but the risk must be considered in vaccine trials.

The exploration of whether genetic variation of SARS-CoV-2 could impact vaccine development is only just beginning. The genome of SARS-CoV-2 is relatively stable compared to many other RNA viruses, but it's been suggested that the emergence of a spike protein variant containing a particular mutation (D614G) could affect recognition by vaccine-induced antibodies. One research paper has offered evidence that this D614G variant might be more transmissible, but the methodology has been questioned by other scientists and the results are considered preliminary; additional studies are ongoing. Encouragingly, the latest studies indicate that SARS-CoV-2 variants with the D614G mutation remain susceptible to antibody responses induced by viruses lacking the mutation.

Concerns have been raised about the possibility of reinfection with SARS-CoV-2. Initially, this was based on anecdotal reports but there are now two cases where researchers have documented compelling evidence of reinfection based on genetic sequencing of the viruses responsible for the first and second infections. The frequency of the phenomenon and implications for vaccines are as yet unclear.

Vaccine Trials

The first SARS-CoV-2 vaccine trial to get underway in the U.S. is evaluating a candidate developed by the company Moderna in collaboration with the National Institutes of Health (NIH) Vaccine Research Center (VRC). The vaccine, mRNA-1273, uses messenger RNA encoding the SARS-CoV-2 spike protein to produce this antigen inside the body. Researchers modified the gene encoding the spike protein to enhance the induction of neutralizing antibodies using a technique initially developed using the coronavirus HKU1 (see the excellent videocast presentation by Barney Graham from the VRC for details). Breaking all previous records, the clinical trial began just 66 days after the genetic code for SARS-CoV-2 became available.

Moderna reported preliminary results from the phase I study in a press release on May 18, 2020, with a more detailed publication following in the *New England Journal of Medicine* on July 14, 2020. A total of 45 participants were evenly divided into three groups and assigned to receive vaccine doses of 25 µg, 100 µg or 250 µg administered twice, about a month apart. Three participants were withdrawn prior to the second immunization, one in the 25 µg group because of urticaria (hives) on both legs and two in the 250 µg group due to suspected COVID-19 (tests ultimately proved negative).

Neutralizing antibody responses were successfully induced after the second immunization, with the highest levels in the 100 µg and 250 µg dose groups. These levels were slightly higher than the average observed in a neutralizing antibody panel obtained from people recovered from COVID-19. So far data are only available out to 57 days but additional follow up is ongoing.

CD4 T cell responses against the SARS-CoV-2 spike protein were documented in the 25 µg and 100 µg dose groups, with low-level CD8 T cell responses also evident in the 100 µg group. The CD4 T cell responses displayed Th1 (T-helper type 1) properties, meaning a bias toward production of certain cytokines. The authors note that there is evidence that this type of response is less likely to be associated with immune-mediated disease enhancement.

The vaccine was generally safe and well tolerated but three participants in the 250 µg group experienced grade 3 systemic symptoms, leading to the discontinuation of this dose. Only one recipient of the 100 µg dose had a grade 3 adverse reaction, consisting of

erythema at the injection site. The most common adverse event was pain at the injection site.

In a commentary accompanying the publication, Penny Heaton states: “These preliminary findings represent the first of three reports of data from a phase 1 study of this candidate vaccine; a second report including similar data from adults older than 55 years of age and a final report summarizing the safety and durability of immunity for both study cohorts are also planned.” Heaton also emphasizes that the link between neutralizing antibody responses and protection is as yet unproven in humans and will need to be assessed in efficacy trials.

Moderna has also reported results from a preclinical mouse challenge experiment in which the vaccine prevented viral replication in lung tissue. A challenge study in macaques (published in the *New England Journal of Medicine*) demonstrated that vaccination was associated with rapid suppression of viral replication and protection against disease.

A 600-person phase II study is now underway at multiple U.S. sites. A 30,000-person phase III efficacy trial employing two injections of the 100 µg dose opened to enrollment in the U.S. on July 27, 2020. As of September, Moderna has reported that the trial is more than halfway enrolled, with around 20% of participants from Black or African American, Latinx, American Indian, and Alaskan Native communities (representation that is far from optimal given the demographics of the COVID-19 pandemic in the U.S.).

The original clinical trial registry entry for the phase III trial indicated that people with HIV would be excluded even though individuals on antiretroviral therapy (ART) with suppressed viral loads and healthy CD4 T counts can respond to vaccination. After requests from advocates and medical professionals, Moderna has announced that they’re removing this exclusion criteria.

Another vaccine undergoing efficacy testing is a chimpanzee adenovirus vector encoding the SARS-CoV-2 spike protein created by researchers at University of Oxford (formerly known as ChAdOx1 nCoV-19, now named AZD1222). As mentioned above, researchers have published a preprint reporting protection against disease after a single dose in a macaque challenge study. The vaccine platform has the advantage of having shown safety in prior human studies for malaria and the coronavirus MERS-CoV.

A phase I/II trial of AZD1222 is ongoing. On May 22, 2020, the University of Oxford announced the launch of a phase II/III efficacy trial in the United Kingdom (UK) with a target enrollment of 10,260 participants. Volunteers will receive either a single vaccine dose or two doses spaced four weeks apart. Researcher Sarah Gilbert has stated that healthcare workers will be targeted for enrollment due to their higher risk exposure to SARS-Co-2. Efficacy trials are also now underway in Brazil and South Africa. The South

African trial includes a component that will assess the safety and immunogenicity of the vaccine in people with HIV on ART. The initiation of a 30,000-person efficacy trial in the U.S. was announced on August 31, 2020.

The first results from the phase I/II trial of AZD1222 were published in the *Lancet* on July 20, 2020. The vaccine appeared safe based on data from 1,077 participants assigned to receive either AZD1222 or a licensed meningococcal vaccine (MenACWY). The MenACWY vaccine was used as a comparator to avoid the possibility that the lack of any typical vaccine reactions to an inert placebo would undermine the goal of blinding study participants as to whether they were receiving AZD1222. Participants were aged 18-55 years, the majority were white and around half were women.

The most commonly reported adverse events were transient local injection site pain and tenderness, which could be ameliorated to some extent by prophylactic paracetamol (started before the injection and maintained for 24 hours). The most frequent systemic reactions were transient fatigue and headache. No serious adverse events were associated with AZD1222.

The paper reports data on levels of antibodies against the SARS-CoV-2 spike protein (measured by an ELISA assay) for 127 AZD1222 recipients. The levels peaked at day 28 after a single immunization and remained elevated at day 56, the last available follow up timepoint. In a small group of ten participants who received two vaccine doses given four weeks apart, antibody levels were higher at day 56 and appeared more comparable to the average observed in control samples from people who had recovered from COVD-19.

The researchers conducted laboratory assessments of neutralizing antibody responses in a subset of AZD1222 recipients. Neutralizing activity was observed in the majority but was more consistent among those who received two doses of the vaccine. There was a good correlation between neutralizing antibody responses and antibody levels measured by ELISA. The AZD1222 vaccine also induced T cell responses targeting the SARS-CoV-2 spike protein, consistent with other studies of the ChAdOx1 vector.

The Chinese company CanSino is developing a candidate using a viral vector derived from human adenovirus serotype 5 (Ad5). Detailed results from phase I testing were published in the *Lancet*, demonstrating induction of low-level antibody responses to the SARS-CoV-2 spike protein after a single injection. The majority of recipients displayed virus-specific T cell responses. Transient fevers and injection site pain were the most common adverse events.

A subsequent publication in the *Lancet* has provided data from a larger phase II evaluation comparing two different single doses of the vaccine to placebo in several hundred participants. Safety findings were similar to the earlier study, with no serious adverse

events. The majority of vaccine recipients displayed binding antibodies against the SARS-CoV-2 spike protein as measured by ELISA, but only around half developed neutralizing antibody responses (assessed with a laboratory assay that measures neutralization of live virus). Virus-specific T cell responses were induced in approximately 90% of vaccine recipients.

Pre-existing immunity to Ad5—which circulates widely in nature in its natural form—was associated with decreased immunogenicity and decreased adverse reactions in both studies. The researchers note that an HIV vaccine candidate based on an Ad5 vector was discontinued after it was found to increase HIV acquisition risk. Although it's uncertain if this effect might be seen with Ad5 vectors containing other antigens, HIV incidence will be monitored in future studies of CanSino's Ad5 vector.

On June 29, 2020, CanSino announced that the vaccine has received "Military Specially-needed Drug Approval" for a provisional period of one year, with use restricted to the Chinese military. The approval is based on safety and immunogenicity data from the published phase I trial and a phase II trial from which results have not yet been publicly presented—there is no data on efficacy in humans. The company is in the process of launching an efficacy trial in multiple countries including Saudi Arabia and Russia.

Several inactivated virus vaccines are emerging from China, with news reports indicating that manufacturing is being scaled up for the candidate being developed by Sinopharm. Researchers have published results from phase I and II studies in a paper in *JAMA*, reporting a low incidence of adverse events (mainly injection site pain and fever) and induction of neutralizing antibodies in recipients of a series of either two or three injections. According to *Bloomberg News*, the vaccine is being offered on an optional basis to employees of some State-run Chinese companies who are planning on traveling abroad for work. An efficacy trial has begun in the United Arab Emirates.

Another Chinese company, SinoVac, has reported safety and immunogenicity results for their inactivated vaccine candidate CoronaVac in a preprint paper. Among 600 participants in a phase I/II trial, adverse events were infrequent—primarily consisting of injection site pain—and none were grade three or above. Neutralizing antibody responses were observed in more than 90% of recipients, but titers were lower than has been reported for other candidates and convalescent plasma (direct comparisons are difficult due to potential technical differences in how testing is performed).

SinoVac has reached a collaborative agreement with Instituto Butantan to launch a phase III efficacy trial in Brazil. The study will evaluate a dosage of 3 μg given on days 0 and 14 or days 0 and 28. News reports indicate that the vaccine has recently been granted emergency use approval for administration to high risk groups in China.

The first data from trials of several mRNA vaccine candidates being developed by BioNTech and Pfizer have been published in the journal *Nature*. After two doses spaced 21 days apart, recipients of the BNT162b1 mRNA vaccine displayed neutralizing antibody titers that were around 2- to 3-fold higher than a comparison panel from people who'd recovered from COVID-19. Adverse events were mostly mild to moderate and transient. A follow up preprint report from a parallel trial conducted in Germany includes additional data on the induction of Th1 T cell responses by the vaccine.

Pfizer has announced that BNT162b2, which encodes an optimized version of the whole SARS-CoV-2 spike protein, has been chosen for efficacy trials due to superior immunogenicity and fewer side effects, particularly in older recipients (results described in another preprint). News reports indicate a phase II/III efficacy trial has been launched at sites in Argentina, Brazil, Germany and the U.S. In an echo of the situation that occurred with Moderna, the trial originally excluded all people with HIV, hepatitis B or hepatitis C, but the company has agreed to amend the protocol to address this issue. The latest reports indicate that the trial is more than halfway toward enrolling the 30,000-person target, but Black, Hispanic and Asian participants represent less than a quarter of the total.

The company INOVIO has provided preliminary and less detailed information from the phase I trial of its DNA vaccine candidate INO-4800 via press release. Induction of both T cell and antibody responses is reported in the majority of recipients, with no significant adverse events. Results from a macaque challenge study are available in a preprint publication: two doses of intradermal vaccine given four weeks apart led to reduced viral load in lungs after a SARS-CoV-2 challenge (administered three months after the last immunization, a longer period than in other vaccine challenge experiments).

Two recombinant protein-based vaccines are entering clinical testing, one developed by Novavax and the other by Clover Biopharmaceuticals.

Novavax has stated that high titers of neutralizing antibodies were induced by their candidate in preclinical non-human primate studies. The vaccine (named NVX-CoV2373) comprises a recombinant SARS-CoV-2 spike protein delivered with a proprietary Matrix-M1 adjuvant, given as two doses spaced 21 days apart. Phase I trial results were published in a journal preprint on August 6, 2020, and the optimal regimen induced neutralizing antibody levels approximately four-fold higher than a comparison sample from people who'd recovered from COVID-19. A 1,500-person phase II study is now underway, and an efficacy trial has been launched in South Africa.

Imperial College London have launched the first trial of a "self-amplifying" mRNA vaccine developed by Robin Shattock. The construct is designed to propagate after injection with the aim of enhancing immune responses to the encoded SARS-CoV-2 spike protein antigen. The vaccine induced high titers of neutralizing antibodies in preclinical mouse

experiments. Imperial College and Morningside Ventures have formed a social enterprise named VacEquity Global Health (VGH) to make the vaccine available cheaply for low-income countries, if it proves successful.

On July 30, 2020, Johnson & Johnson announced the initiation of clinical trials of their COVID-19 vaccine candidate. The vaccine uses an adenovirus serotype 26 (Ad26) vector to deliver a full-length SARS-CoV-2 spike protein. In tandem with the announcement, results from a macaque challenge study were published in the journal *Nature*. Several Ad26 vectors encoding slightly different forms of SARS-CoV-2 proteins were tested, with the most robust protection from infection observed among animals immunized with the full-length SARS-CoV-2 spike protein that's now being advanced into human testing.

In Moscow, the Gamaleya Research Institute of Epidemiology and Microbiology is testing Ad5 and Ad26 vectors encoding the SARS-CoV-2 spike protein. No data has been made available publicly, but the Russian equivalent of an emergency use authorization has been granted for limited distribution within the country prior the availability of efficacy results (some media reports have mistakenly characterized this development as equating to full approval of the vaccine). Efficacy trials are now being initiated.

A fleet of other candidates are swelling the pipeline of vaccines in clinical trials. A broad range of approaches are represented including DNA and mRNA-based delivery, viral vectors, recombinant proteins, and inactivated virus vaccines (see table below).

An alternative approach to inducing protection against SARS-CoV-2 involves the use of the ancient Bacillus Calmette–Guérin (BCG) vaccine, originally created to prevent tuberculosis. One preliminary ecological study has suggested that there might be an association between receipt of BCG and reduced mortality from COVID-19, but as TAG has explained in a statement, results from controlled trials are needed to determine if there is a real effect. Several trials are now ongoing.

Human Challenge Studies

A controversial proposal for speeding up efficacy testing of SARS-CoV-2 vaccines is the use of human challenge trials (deliberate infection of vaccine recipients with SARS-CoV-2). The idea is based on the notion that young individuals are at a relatively low risk for serious complications and therefore such studies could be ethically justified. These claims are debatable, at best, because there are so many unknowns about the pathogenesis of COVID-19. Recent anecdotal reports of clotting problems and strokes in young people with COVID-19 emphasize how much remains to be learned.

Despite the uncertainties, and without any evident public notice or community consultation, WHO has issued a report delineating potential criteria for initiating human challenge

experiments. Similarly, the NIH held a consultative meeting on the topic on May 11th, publicly disclosed only the day before in a news article in the *Financial Times*. TAG and AVAC have issued a joint statement raising concerns about both the ethics of human challenge studies and the lack of transparency and consultation regarding their possible implementation. Ethicist Ruth Macklin has also published a critique of the proposal, concluding that "a rush to begin human challenge studies for a grave disease lacking an effective treatment is ethically unjustifiable." Macklin's views are echoed in a more recent paper by Liza Dawson and colleagues.

In a troubling and disappointing development, the lead researcher for the Oxford AZD1222 vaccine, Adrian Hill, has stated that they plan to conduct human challenge experiments before the end of 2020. Given that efficacy trials are already underway, there appears to be little justification for deliberately exposing volunteers to the risk of COVID-19. TAG, AVAC and other organizations have issued a statement opposing the use of challenge experiments at this time. The National Institute of Allergy and Infectious Diseases (NIAID) has reported that challenge strains of SARS-CoV-2 are being prepared in the U.S. but only as a contingency plan in case the incidence of COVID-19 declines to levels that preclude the conduct of traditional efficacy trials.

Making a Vaccine Available

The U.S. Food and Drug Administration (FDA) has issued detailed guidance for industry on the development and licensure of vaccines to prevent COVID-19. The agency states that efficacy of at least 50% would be required for approval. Safety information would also be needed from large numbers (>3,000) of study participants for at least six months after completion of all immunizations. In some cases, longer safety monitoring might be requested (an example given is for vaccines that include novel adjuvants). These regulatory requirements preclude the possibility of any COVID-19 vaccines receiving full FDA approval before the end of 2020.

The guidance offers less clarity regarding the possibility of issuing Emergency Use Authorizations (EUAs) for COVID-19 vaccine candidates, but notes: "for a vaccine for which there is adequate manufacturing information, issuance of an EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before the manufacturer has submitted and/or FDA has completed its formal review of the biologics license application."

There are concerns about the potential for FDA to be politically pressured into announcing a vaccine "October surprise" to help with the current U.S. President's flailing reelection campaign.

Agency representatives—including commissioner Stephen Hahn—have published an article in *JAMA* stating they're "committed to ensuring that any vaccine is manufactured in accordance with all of FDA's quality standards and that its safety and effectiveness are verified before being authorized or licensed." Hahn's credibility has been severely damaged, however, by the FDA's granting of an EUA to convalescent plasma as a therapy (see the treatment pipeline page). In announcing the EUA, Hahn made false claims about the efficacy of the approach and only belatedly acknowledged the mistake.

Several lines of evidence intimate the possibility of a pre-election EUA in the U.S. Hahn himself has not ruled out the idea. The *Financial Times* has reported that AZD1222 might be considered based on results (as yet unknown) from the ongoing efficacy trial in the U.K. Perhaps most worryingly, the Director of the Centers for Disease Control and Prevention (CDC) has written to State governors requesting that plans be in place for distribution of a vaccine by November 1, 2020. As reported in the *New York Times*, associated CDC documentation suggests that it is the Moderna and Pfizer vaccines that are being considered, but it is very difficult to imagine a scenario in which sufficient efficacy data would be available.

This situation will need to be carefully monitored. The Director of the FDA's Center for Biologics Evaluation and Research (CBER), Peter Marks, has stated that he will resign if he feels politically pressured to grant authorization to a vaccine with inadequate safety and efficacy data.

FDA regulations only apply to the U.S., there are ongoing efforts to promote global coordination through the International Coalition of Medicines Regulatory Authorities; for example, the coalition recently issued a report on the conduct of phase III vaccine efficacy trials.

If the scientific challenge of developing a SARS-CoV-2 vaccine can be addressed, more practical issues of manufacturing capacity, cost and global access will come to fore, and it is critical to consider these issues now. Bill Gates has outlined plans to develop manufacturing capacity for multiple experimental candidates in order to be ready if one or more should work. Johnson & Johnson has committed to scale up manufacturing so that global distribution can happen quickly and "at cost" if efficacy is demonstrated. In an advance purchase deal with the U.S. government worth over US$1 billion, the company has agreed a price of around US$10 per dose.

The Oxford University research group is securing non-exclusive manufacturing agreements for their candidate with multiple companies including the Serum Institute of India, a major global supplier of vaccines, and AstraZeneca, who've agreed to distribute worldwide. The U.S. government has entered into a contract with AstraZeneca to secure 300 million doses in exchange for the provision of up to $1.2 billion in funding support.

Additional U.S. government agreements include a $1.95 billion contract with Pfizer to purchase supplies of their vaccine if it proves effective, at a maximum price of $19.50 per dose ($39.00 per person for the two-shot regimen). Sanofi and GlaxoSmithKline have received a funding commitment of up to $2.1 billion to support both vaccine research and eventual product purchases (no price specified).

The highest vaccine price quoted to date comes from Moderna, who are said to be negotiating advance orders at around US$32 to $37 per dose (a slightly lower price has been negotiated for the U.S.). This is despite the fact that they've stated that their research program is essentially 100% supported by U.S. government funds, with significant contributions to the vaccine design coming from scientists at the NIH's Vaccine Research Center (these scientists have filed patent applications related to their work on the construct, see the competing interests section of their paper in *Nature*).

The Serum Institute of India has announced a partnership with Gavi and the Bill & Melinda Foundation to produce up to 100 million doses of both the Oxford/AstraZeneca and Novavax vaccines at a maximum price of US$3 per dose for low and middle-income countries.

Discussions are now starting regarding how distribution of an effective vaccine (or vaccines) might be prioritized given that initial supplies would likely be limited. The National Academies of Sciences, Engineering, and Medicine has invited public comment on a draft "Preliminary Framework for Equitable Allocation of COVID-19 Vaccine." The Johns Hopkins Center for Health Security has also published an Interim Framework for COVID-19 Vaccine Allocation and Distribution in the U.S.

Experts have strongly cautioned that "vaccine nationalism"—in which countries like the U.S. focus solely on securing supplies for their own population—could have devastating consequences for efforts to ensure global access. Despite these warnings, wealthy countries have already rushed to make advance orders for more than two billion vaccine doses, raising the specter of the all-too-common situation in which resource-limited settings are left behind.

U.S. Development Efforts and Global Context

The U.S. government contracts are part of a project to accelerate the development and distribution of SARS-CoV-2 vaccines dubbed Operation Warp Speed (see article in *Science* by Jon Cohen). The aim is to have 300 million doses of an effective product by January 2021, but only for use in the U.S. The operation appears steeped in the Trump administration's dismal "America First" rhetoric and is excluding Chinese vaccine candidates without any apparent scientific rationale—likely due to the president's rancidly

xenophobic and predictable effort to blame China for his disastrous mismanagement of the COVID-19 crisis.

Operation Warp Speed represents a public-private partnership between various U.S. government agencies and industry. A key player is the NIH-initiated Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program, another public-private collaboration. To facilitate vaccine evaluation, two HIV research networks—the HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN)—will glom together with the Infectious Diseases Clinical Research Consortium (IDCRC) to form the CoV Prevention Network (CoVPN).

Several vaccine development efforts have been reported to be receiving support through Operation Warp Speed, but U.S. government officials have declined to provide a full list, reflecting an appalling lack of transparency about the program:

- Moderna's mRNA candidate.
- The University of Oxford/AstraZeneca AZD122 chimpanzee adenovirus vector.
- Pfizer's mRNA candidate (currently entering phase II/III, see table). The company is part of the program but not accepting government funding to support research.
- Johnson & Johnson's Ad26 vector.
- Merck, which is pursuing a recombinant vesicular stomatitis virus (rVSV) vector in collaboration with IAVI and an attenuated measles virus vector developed by the company Themis.
- Novavax's recombinant protein vaccine.

As explained in an excellent review by John P. Moore and P. J. Klasse, these candidates mainly represent either viral vector or mRNA delivery systems, neither of which may be optimal for the induction of antibody responses. Protein-based or inactivated virus vaccines have a better track record for creating high levels of antibodies, but whether that would be important for protection against COVID-19 is not yet known. Moore and Klasse also emphasize the short-sightedness of taking a nationalistic approach to vaccine development and argue for the importance of international collaboration. For example, it might turn out that there are advantages to combining candidates of different types and currently China is the only country producing inactivated vaccines.

The U.S. has refused to take part in a global vaccine development effort brought together by the WHO, another entity onto which Trump has tried to place blame for the COVID-19 pandemic. The WHO (ACT) Accelerator collaboration aims to speed the arrival of an effective vaccine and recently announced a plan to purchase 2 billion doses of COVID-19 vaccines for the highest risk populations globally via the COVID-19 Vaccines Global Access (COVAX) Facility (in partnership with the Coalition for Epidemic Preparedness Innovations and Gavi, the Vaccine Alliance).

Beyond some mumbled and unconvincing comments at the official launch of Operation Warp Speed, the U.S. government's commitment to global collaboration on provision of access appears questionable, at best. The U.S. repudiated language in a World Health Assembly resolution that highlights options to override intellectual property rights in order to promote access to COVID-19 vaccines and treatments (the resolution was adopted and is being finalized). On September 1, 2020, the U.S. government formally announced that they won't be participating in the COVAX initiative - it would run counter to Trump's effort to scapegoat WHO for his failures.

UNAIDS and Oxfam have coordinated a call for a "people's vaccine" by over 140 world leaders, experts and elders. The call seeks guarantees that COVID-19 vaccines, diagnostics, tests and treatments will be provided free to all who need them. The African Union has also issued a strong statement emphasizing the "urgent need for countries to make full use of legal and policy measures, including flexibilities enshrined under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and Doha Declaration, South-South and North-South collaboration to ensure monopolies do not stand in the way of access to COVID-19 vaccines."

Community Participation

Community involvement in vaccine research is well established for HIV and a growing part of the research effort for other diseases. The urgency and rapidity of vaccine discovery for SARS-CoV-2 makes creation of similar processes challenging, but it is vital that there is broad stakeholder input into the range of issues likely to affect the development and rollout of an effective candidate—including efficacy testing, safety, practicality, effectiveness across different populations, cost and global access. Stakeholders must include the communities most heavily impacted by the disease and civil society activists with experience in issues of vaccine research and development. Researchers involved in both ACTIV and the CoV Prevention Network have begun communicating with community-based partners to seek input regarding their plans.

Pipeline Table

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
AZD1222 (formerly ChAdOx1 nCoV-19)	Chimpanzee adenovirus vector expressing the SARS-CoV-2 spike protein	NCT04536051 NCT04516746 ISRCTN89951424 (Active, not recruiting) NCT04400838 NCT04444674 NCT04324606 (Active, not recruiting)	University of Oxford, AstraZeneca	Phase III Phase II/III Phase I/II
CoronaVac	Inactivated SARS-CoV-2	NCT04508075 NCT04456595 NCT04383574 (Active, not recruiting) NCT04352608 (Active, not recruiting)	Sinovac Biotech Co., Ltd.	Phase III Phase I/II
mRNA-1273	mRNA vaccine encoding SARS-CoV-2 spike protein	NCT04470427 NCT04405076 (Active, not recruiting) NCT04283461 (Active, not recruiting)	Moderna	Phase III Phase IIa Phase I
Inactivated SARS-CoV-2 Vaccine	Inactivated SARS-CoV-2	ChiCTR2000034780 NCT04470609 NCT04412538	Chinese Academy of Medical Sciences	Phase III Phase Ib/IIb Phase Ia/IIa

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
Inactivated 2019-CoV vaccine (Vero cells)	Inactivated SARS-CoV-2	NCT04510207 ChiCTR2000031809 ChiCTR2000032459	Wuhan Institute of Biological Products/Sinopharm	Phase III Phase I/II
Ad5-nCoV	Adenovirus serotype 5 (Ad5) vector expressing the SARS-CoV-2 spike protein	NCT04526990 (Not yet recruiting) NCT04341389 (Active, not recruiting) NCT04398147 (Not yet recruiting) NCT04313127 (Active, not recruiting)	CanSino Biologicals /Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	Phase III Phase II Phase I/II Phase I
Ad26.COV2.S	Adenovirus serotype 26 (Ad26) vector encoding full-length SARS-CoV-2 spike protein	NCT04436276 (Not yet recruiting) NCT04509947 NCT04436276	Janssen Vaccines & Prevention B.V./ Janssen Pharmaceutical K.K.	Phase III Phase I/IIa
BNT162b2	mRNA vaccine candidate expressing optimized whole SARS-CoV-2 spike protein	NCT04368728	BioNTech RNA Pharmaceuticals GmbH/Pfizer	Phase II/III
SARS-CoV-2 rS	Recombinant spike protein nanoparticle vaccine +/- Matrix-M adjuvant	NCT04533399 NCT04368988	Novavax	Phase II Phase I
GX-19	DNA vaccine expressing the SARS-CoV-2 spike protein	NCT04445389	Genexine, Inc.	Phase I/IIa

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INO-4800	DNA vaccine expressing the SARS-CoV-2 spike protein, delivered intradermally followed by electroporation	NCT04447781 NCT04336410 (Active, not recruiting)	Inovio Pharmaceuticals	Phase I/IIa Phase I
CVnCoV	mRNA vaccine encoding SARS-CoV-2 spike protein	NCT04515147 (Not yet recruiting) NCT04449276	CureVac AG	Phase IIa Phase I
AV-COVID-19	Autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CSF	NCT04386252 (Not yet recruiting)	Aivita Biomedical, Inc.	Phase Ib/II
Gam-COVID-Vac	Ad5 and Ad26 vectors expressing the SARS-CoV-2 spike protein	NCT04436471 (Completed)	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Phase I/II
Gam-COVID-Vac Lyo	Ad5 and Ad26 vectors expressing the SARS-CoV-2 spike protein, lyophilized	NCT04437875 (Active, not recruiting)	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Phase I/II
EpiVacCorona	Peptide-based vaccine	NCT04527575 (Active, not recruiting)	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	Phase I/II
BNT162a1 BNT162b1 BNT162b2 BNT162c2	Four variants of a messenger RNA (mRNA) vaccine candidate expressing either the SARS-CoV-2 spike protein or the receptor binding domain (RBD) from the spike protein	NCT04380701 NCT04368728	BioNTech RNA Pharmaceuticals GmbH/Pfizer	Phase I/II

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AG0301-COVID19	DNA vaccine	NCT04527081 NCT04463472 (Active, not recruiting)	AnGes, Inc.	Phase I/II
ZyCoV-D	DNA vaccine	CTRI/2020/07/026352	Cadila Healthcare Ltd.	Phase I/II
BBV152 (Covaxin)	Whole-virion inactivated SARS-CoV-2 vaccine	NCT04471519	Bharat Biotech International Ltd.	Phase I/II
KBP-201	Tobacco plant-derived recombinant protein vaccine	NCT04473690 (Not yet recruiting)	Kentucky BioProcessing, Inc.	Phase I/II
ARCT-021	Self-replicating (replicon) mRNA encoding the SARS-CoV-2 prefusion spike protein formulated in a lipid nanoparticle (LNP)	NCT04480957	Arcturus Therapeutics, Inc.	Phase I/II
QazCovid-in®	Inactivated SARS-CoV-2	NCT04530357	Research Institute for Biological Safety Problems	Phase I/II
LV-SMENP-DC	Dendritic cells transduced with a lentiviral vector expressing selected virus proteins and immunomodulatory genes administered together with virus-specific CD8 T cells	NCT04276896	Shenzhen Geno-Immune Medical Institute	Phase I
Pathogen-specific aAPC	Artificial antigen-presenting cells (aAPCs) transduced with a lentiviral vector expressing selected virus proteins and immunomodulatory genes	NCT04299724	Shenzhen Geno-Immune Medical Institute	Phase I
bacTRL-Spike-1	Live Bifidobacterium longum engineered to deliver DNA expressing the SARS-CoV-2 spike protein	NCT04334980 (Not yet recruiting)	Symvivo Corporation	Phase I

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SCB-2019	Recombinant SARS-CoV-2 trimeric spike protein subunit vaccine +/- AS03 adjuvant or CpG 1018 + Alum adjuvant	NCT04405908	Clover Biopharmaceuticals AUS Pty Ltd.	Phase I
Coronavirus-like particle COVID-19 vaccine	Virus-like particle	NCT04450004 (Active, not recruiting)	Medicago	Phase I
Recombinant novel coronavirus vaccine	Adjuvanted recombinant protein	NCT04466085 NCT04445194	Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.	Phase I
LNP-nCoVsaRNA	Self-amplifying RNA expressing the SARS-CoV-2 spike protein encapsulated in lipid nanoparticles	ISRCTN17072692	Imperial College London	Phase I
ARCoV	mRNA expressing SARS-CoV-2 proteins	ChiCTR2000034112 (Not yet recruiting)	People's Liberation Army Academy of Military Sciences/Yunnan Walvax Biotechnology Co., Ltd.	Phase I
COVAX19	COVID19 recombinant spike protein with Advax-SM adjuvant	NCT04453852	Vaxine Pty Ltd.	Phase I
UQ-1-SARS-CoV-2-Sclamp	Adjuvanted SARS-CoV-2 Sclamp protein subunit vaccine	NCT04495933	University of Queensland	Phase I
MVC-COV1901	SARS-CoV-2 spike protein with CpG 1018 + aluminum content adjuvant	NCT04487210 (Not yet recruiting)	Medigen Vaccine Biologics Corp.	Phase I
TMV-083	Live-attenuated recombinant measles vaccine virus vector expressing a modified SARS-CoV-2 surface glycoprotein	NCT04497298	Institut Pasteur/ Themis Bioscience GmbH	Phase I

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V591	Live-attenuated recombinant measles vaccine virus vector expressing a modified SARS-CoV-2 surface glycoprotein	NCT04498247 (Not yet recruiting)	Merck Sharp & Dohme Corp.	Phase I
Recombinant SARS-CoV-2 vaccine (Sf9 cell)	Recombinant SARS-CoV-2 spike protein	NCT04530656 (Not yet recruiting)	Jiangsu Province Centers for Disease Control and Prevention	Phase I
GRAd-COV2	Gorilla adenovirus vector encoding the SARS-COV-2 spike protein	NCT04528641	ReiThera Srl	Phase I
BNT162b1	mRNA vaccine encoding trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain	NCT04523571	BioNTech RNA Pharmaceuticals GmbH	Phase I
AdimrSC-2f	Recombinant protein subunit vaccine	NCT04522089	Adimmune Corporation	Phase I