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A Vexing Virus and The Valuation of Vaccines

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Insights

- The scientific community and vaccine industry have come together to develop a vaccine for COVID-19 at remarkable speed.
- As of July 24, 2020, there have been 25 and 141 vaccine candidates in clinical evaluation and pre-clinical evaluation, respectively.
- A wide range of platforms are used for the vaccine candidates, including DNA, inactivated, live attenuated virus, nonreplicating viral vector, protein subunit, replicating viral vector, RNA, and Virus Like Particles (VLP).
- Several vaccine candidates are ready for Phase 3 trials, yet it is unlikely that any of them will become available before the end of 2020.
- Vaccine trials typically take several years to conduct – the difficulty of accomplishing this task in a few months have been echoed across the scientific community.
- There are a wide range of challenges pertaining to the development, licensing, manufacturing, and dissemination process before a vaccine can become available at the population level.
- The current approach to distributing a future vaccine in an equitable manner around the world can be described as piecemeal at best – with low- and middle-income countries at great disadvantage of accessing the vaccine at the same time as wealthier nations.

The rush for a cure for COVID-19

"We're already starting the process of allocating vaccine vials to a variety of different clinical sites in the US and elsewhere…we're looking at the map and getting good advice from the CDC."

Mikael Dolsten
Chief Scientific Officer, Pfizer (1)

Since the outbreak of the COVID-19 pandemic, there has been an enormous global effort to develop vaccines against the coronavirus SARS-CoV-2. Vaccines play a critical role in achieving long-term prevention and control of the virus (2). Most recently, https://www.coronaviruspreventionnetwork.org/ went live – where individuals in the US can register to participate in clinical trials for vaccines as well as monoclonal antibody therapies. Given the magnitude of the current public health crisis, vaccine trials are moving at an unprecedented speed and trying to accomplish what usually takes years in months. As of July 24, 2020, there have been 25 vaccine candidates in clinical evaluation and 141 candidates in preclinical evaluation (3,4). Yet, there are a myriad of challenges that must be overcome before a vaccine can be available for use and disseminated in an equitable manner. A nuanced understanding of the current state of vaccines for COVID-19 can help governments, health care systems, clinicians, and the public plan for the months to come.

"The SARS and Zika epidemics ended before vaccine development was complete, and federal funding agencies reallocated funds that had been committed to vaccine development, leaving manufacturers with financial losses and setting back other vaccine-development programs."

Lurie et al 2020 (3)

Lessons from EBOLA, Zika, SARS Vaccine Development: Too little, Too Late.

The COVID-19 pandemic is not the first time the scientific community and the vaccine industry have sought to develop a vaccine at rapid speed. In recent history, the outbreak of H1N1 influenza, Ebola, Zika, and severe acute respiratory syndrome (SARS) all required similar action. A vaccine for H1N1 influenza was developed relatively quickly because technology for influenza vaccine was already well developed (3). The monovalent H1N1 vaccine became available soon after the pandemic peaked in the Northern Hemisphere as a stand-alone vaccine (3). However, vaccines for Ebola, Zika, and SARS

2014–2016 outbreak in West Africa was the largest Ebola outbreak since the virus was first discovered in 1976; The virus causing the current outbreak in The Democratic Republic of the Congo and the 2014–2016 West African outbreak belongs to the Zaire ebolavirus species. **Case fatality rate is around 50%**

2015-2016 Zika outbreak that originated in Brazil and spread to more than 50 countries was the largest outbreak of this virus since it was first discovered in 1947. Zika is a flavivirus that is transmitted mainly by mosquitos in the genus Aedes. **Case fatality rate is around 8.3%**

2002-2003 SARS outbreak originated in China and spread to 29 countries. SARS is caused by a coronavirus (SARS-CoV), which was identified in 2003. **Case fatality rate is around 15%**

did not have similar success – none of them were developed before the respective outbreaks ended. Historically, there have been several challenges for taking vaccine candidates to clinical development prior to an outbreak. For example, in the case of Ebola, it was not possible to demonstrate clinical efficacy in the absence of an ongoing outbreak, which was further compounded by the lack of interest from the public health system and vaccine industry to invest in the lengthy and expensive process to develop a vaccine without clear demand (2). Nonetheless, the aftermath of each of the previous pandemics has highlighted the need for novel development-and-manufacturing platforms for vaccines for newly emerging pathogens (3). Given this background, SARS-CoV-2 has arrived at a time of increased scientific understanding and innovation, with a variety of vaccine platforms current being developed.

How Do Vaccines Work?

Vaccines work by giving us a small amount of a harmless form of a disease, which triggers our bodies to create antibodies to fight it off. If we encounter the disease again in the future, our body can use those antibodies that prevent us from getting sick – thus achieving immunity. (Source: British Society for Immunology).

Early Promise From Phase II Results: Vaccines for COVID-19

Below is a summary of the major platforms, which are technologies used to develop vaccines, that are currently being used for COVID-19 vaccine candidates (Exhibit 1) (3,4). Many developers from around the world are working to evaluate these vaccine candidates (Appendix). Both the US and the UK have already made agreements with Pfizer Inc and German biotech BioNTech SE to buy 100 and 30 million doses, respectively, if their RNA-based vaccine, which is gearing up for a Phase 3 trial, proves to be effective (1,5).

EXHIBIT 1: PLATFORMS FOR COVID-19 VACCINE CANDIDATES (3,4)

Type of Vaccine Platform	Licensed Platform	Candidates in Clinical Evaluation	Candidates in Pre-Clinical Evaluation
DNA	No	Yes	Yes
Inactivated	Yes	Yes	Yes
Live Attenuated Virus	Yes	No	Yes
Protein Subunit	No	Yes	Yes
Nonreplicating Viral Vector	Yes	Yes	Yes
Replicating Viral Vector	Yes	No	Yes
RNA	No	Yes	Yes
Virus Like Particles (VLP)	No	Yes	Yes

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*SEE APPENDIX BELOW FOR DEVELOPERS/MANUFACTURERS FOR VACCINE CANDIDATES USING DIFFERENT PLATFORMS

Results of two early phase COVID-19 vaccine trials using a nonreplicating factor have been published – a phase 1/2 trial from the UK with support from AstraZeneca, and a phase 2 trial from China with support from CanSino Biologics (6,7). Both these trials reported the vaccine achieved significant anti–SARS-CoV-2 immune responses. Mild adverse events were reported in both trials, such as fever, fatigue, and injection site pain, but neither trials reported severe adverse events. Results of a phase 1 trial in the US for an RNA-based vaccine developed by Moderna also showed significant immune responses in all participants and no trial limiting safety concerns (8). While these trials show promising results, it will likely take a long time before these vaccines become widely available due to a variety of challenges pertaining to their development, licensing and manufacturing process, and dissemination at the population level.

Phase	Primary Goal
Phase I	Testing of drug on healthy volunteers for safety; involves testing multiple doses (dose-ranging)
Phase II	Testing of drug on patients to assess efficacy and side effects
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety
Phase IV	Testing of drug on patients to assess long term safety and effectiveness

> "We need people who are black and brown and representative of harder hit communities by the pandemic."
>
> **Dr. Carl Fichtenbaum**
> -Medical director of the Moderna trial at University of Cincinnati Health (10)

Clinical trials at pandemic speed

There are many challenges associated with designing, conducting, and completing large and complicated trials very fast. Well-conducted trials are resource intensive – they require funding, trained investigators, research staff, and oversight teams (9). Additionally, it typically takes a year or more to develop trial protocols, recruit collaborators, obtain funding and regulatory approval, and launch the trial (9). The difficulty in accomplishing several years worth of work in a few months has been echoed widely across the scientific community – which questions whether it will indeed be plausible to develop new vaccines in an expedited manner.

As an example, the case of the vaccine developed by Moderna illustrates the many operational challenges of conducting trials during a pandemic. A Phase 3 trial of this vaccine was expected to begin on July 27, 2020. However, Dr. Carlos del Rio, principal investigator at the Moderna site at Emory University in Atlanta, explained "...those target dates move up and down. They won't let a site start until they're absolutely ready. Some could start on July 27, and others on August 8" (10). Although he plans on recruiting participants soon, as of July 9, 2020, he did not receive approval from Emory's Institutional Review Board to begin the trial (10). There is also the added challenge of recruiting large numbers of participants within a short period of time, which on its own may be an unpredictable process. Dr. Richard Novak, who will be leading the Moderna trial at the University of Illinois at Chicago, noted "I've been doing vaccine trials for 25 years, but this is the largest I've ever committed to and I just don't have enough staff and I don't have enough space" (10).

Beyond the operational challenges, there are many study design related challenges that are difficult to address during a pandemic. Current vaccine trials include small numbers of participants thus any inferences must be made with caution. Phase 3 trials need to be conducted for current vaccine candidates on larger populations of participants to examine their efficacy and safety. However, ideal Phase 3 trials should be rapid, pragmatic, and large enough to address efficacy in different subgroups of interest (11). This is particularly relevant for older adults as well as those with comorbidities, who are typically excluded from clinical trials (11). Ethnic diversity is also important to capture – COVID-19 may impact some ethnic and racial groups more severely than others (12-15). It is important to note that the vaccine trials with published results presented above have limited ethnic diversity. These considerations highlight the importance of including large and representative samples in Phase 3 trials, which is difficult to achieve when there is pressure to proceed with research as quickly as possible given a global health crisis.

"Vaccine development is a lengthy, expensive process. Attrition is high, and it typically takes multiple candidates and many years to produce a licensed vaccine…with multiple pauses for data analysis or manufacturing-process checks."

Lurie et al 2020 (3)

Scaling up considerations

While it is reassuring to see several COVD-19 vaccines currently under development, a strong commercialization infrastructure is needed to successfully introduce new vaccines to the market. Proceeding to Phase 3 trials requires manufacturing to be scaled up to commercial levels for large volumes of safety and immunogenicity data to become available (3). In addition to the financial investment, there are added challenges for manufacturing COVID-19 vaccines that use novel platforms, which are not licenced nor have gone through previous large-scale manufacturing (3). These are pressing concerns for the vaccine candidates that are currently gearing up for Phase 3 trials, as they use nonreplicating vectors or RNAs as platforms – neither of which are currently licensed. To have necessary evidence on the safety and efficacy of the new vaccines, a lot has to happen within a short period of time, including identifying facilities that can produce large volumes of product, transferring necessary technologies, and adapting manufacturing processes (3). All these steps may be too ambitious to achieve before the end of 2020 – especially when considering the history of developing vaccines for recent pandemics, where most of the required vaccines were not developed until long after the outbreak was over.

"If we just let drugs and vaccines go to the highest bidders, instead of to the people and the places where they are most needed, we'll have a longer, more unjust, deadlier pandemic,"

Bill Gates, International Aids Society Lecture
July 2020

Access to Vaccines: Who Gets Them First?

One of the most unfortunate consequences of every pandemic is the exacerbation of existing inequalities. During a time of any global crisis, marginalized populations around the world are disproportionately disadvantaged along multiple dimensions, including health, education, and finances. Without equitable access to COVID-19 vaccines, the global disparities between high income and low- and middle-income countries (LMICs) can grow even further. The pandemic has already exposed many challenges that can hinder global governance for vaccines. Not only are there significant gaps in the health care systems in many countries, but the current global governance system is fragmented and does not have the necessary structures to pool and share resources to tackle the pandemic (16). Furthermore, the early days of the pandemic have revealed some concerning trends that question the likelihood of global strategies to preserve health for all – regardless of their country of residence. Medical protectionism has been already observed in many countries when they scrambled to stockpile personal protective equipment and ventilators for their own citizens (16). This mentality could be translated to accessing vaccines when they finally become available – with a real possibility of countries competing against each other for a vaccine bidding war (16).

Ensuring equitable distribution of future vaccines is now a priority for several leading organizations, including Gavi, the Vaccine Alliance. They recently launched the Gavi Covax Advance Market Commitment (AMC) to subsidise doses for lower-income countries (17). The AMC hopes to raise $2 billion dollars to manufacture the first 20 million doses – however, a much bigger budget is required to provide vaccines for all developing countries (17). There are several other initiatives being floated to ensure equitable access to vaccines for all – however, their approach can be described as piecemeal at best. In June 2020, France, Germany, Italy, and the Netherlands formed the Inclusive Vaccine Alliance (IVA) with the goal of making vaccines affordable and accessible to European Union member states (16). The IVA plans to make a portion of the vaccines available to low income countries – yet, it is not clear how big this portion will be or which countries will receive this support (16). There is a second AMC proposal from Harvard University which presents an “America first” model – where investment would be made in manufacturing capacity to vaccinate all Americans first, and the infrastructure created to protect Americans would be offered to the rest of the world after (17). Beyond the lack of equality and transparency engrained in these proposals for low income countries, middle income countries are largely left out from any vaccine access plans. This is hugely concerning as India and Brazil, both middle income countries, show the highest numbers of daily and overall confirmed cases of COVID-19, following the US (Source: Johns Hopkins University).

Even if governments around the world commit to a fair allocation of vaccine agreement, equitable access to vaccines can still be a challenge if their price is high. For example, for Gavi's previous AMC fund for pneumococcal vaccines, pharmaceutical companies have demanded a high price (17). Without global engagement with pharmaceutical companies which calls for open discussion regarding the cost of producing the vaccines and adjusting prices accordingly, the real affordability of a vaccine when it becomes available remains uncertain. If high income countries rush to get access to vaccines as soon as possible without negotiating on a fair price, many of the LMICs can be left without vaccines for an exceedingly long time.

The best course of action is to remain vigilant and engage in preventive practices that minimize the risk of infection, including social distancing, sanitizing, and wearing masks.

We Won't See A Vaccine in 2020: It's A Waiting Game

Even amid one of the greatest public health crises we have experienced in recent history, the progress made by the scientific community and vaccine industry to battle COVID-19 has been remarkable. Developing and commercializing any vaccine is a complex process, and even more so during a virus outbreak that requires urgent action. When there is a pandemic, there are high levels of uncertainty and unpredictability across many dimensions, including unpredictable nature of the virus, unpredictable stakeholders and customers, unpredictable timing of need, as well as unpredictable geographies with increased need (2). While current efforts to introduce a COVID-19 vaccine to the public before the end of 2020 is commendable, it is unlikely to become a reality. In the meantime, the best course of action is to remain vigilant and engage in preventive practices that minimize the risk of infection, including social distancing, sanitizing, and wearing masks. Governments, health care systems, and clinicians can continue to enforce and promote these practices in their local settings to curb the pandemic in the foreseeable future.

OE Community Perspectives on COVID-19 Vaccines

We conduced a poll within the OE community to gain their perspectives on COVID-19 vaccines. Overall, 74% of participants voted that vaccines should be given first to those at highest risk (Exhibit 2). In terms of the time when a vaccine would be available, 71% of participants indicted that they feel a vaccine will be ready sometime in 2021 (Exhibit 2). For vaccine distribution around the world, 47% of participants indicated that developed and developing nations should get access at the same time, even if it means that not everybody in every country will have a full supply (Exhibit 3).

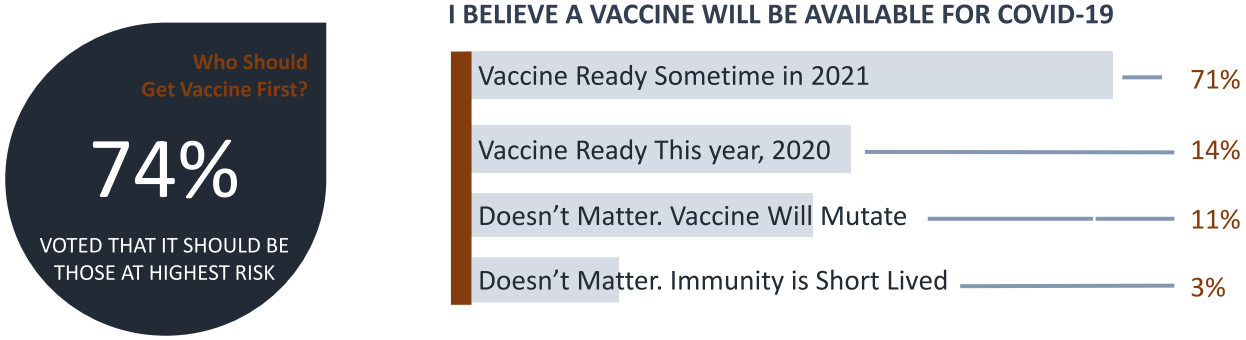

Exhibit 2: COVID-19 Pandemic Vaccine. OrthoEvidence Random Sampling N=43

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HOW SHOULD COVID-19 VACCINES BE DISTRIBUTED AROUND THE WORLD?

- Countries with highest infection rates first
- Countries with resources to pay for the cost of vaccines
- Low and middle income countries with limited ability to physical distance
- Developed/Developing Nations should get access at the same time, even if that means not everyone will have full supply

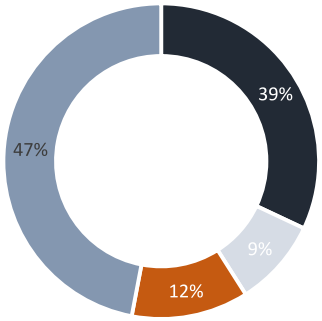

Exhibit 3: COVID-19 Pandemic Vaccine. OrthoEvidence Random Sampling N=43

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Appendix

Type of Vaccine Platform

	DNA	Inactivated	Live Attenuated Virus	Nonreplicating Viral Vector
Vaccine Developer/ Manufacturer	Inovio Pharmaceuticals/ International Vaccine Institute; Osaka University/ AnGes/ Takara Bio; Cadila Healthcare Limited; Genexine Consortium; Ege University; Scancell/University of Nottingham/ Nottingham Trent University; National Research Centre, Egypt; Karolinska Institute / Cobra Biologics (OPENCORONA Project); Chula Vaccine Research Center; Takis/Applied DNA Sciences/Evvivax; Immunomic Therapeutics, Inc./EpiVax, Inc./PharmaJet; BioNet Asia; Mediphage Bioceuticals/University of Waterloo; Entos Pharmaceuticals; Symvivo	Sinovac; Wuhan Institute of Biological Products/Sinopharm; Beijing Institute of Biological Products/Sinopharm; Institute of Medical Biology, Chinese Academy of Medical Sciences; Bharat Biotech; KM Biologics; Selcuk University; Erciyes University; National Research Centre, Egypt; Beijing Minhai Biotechnology Co., Ltd; Osaka University/ BIKEN/ NIBIOHN; Sinovac/Dynavax; Valneva/Dynavax; Research Institute for Biological Safety Problems, Rep of Kazakhstan	Mehmet Ali Aydinlar University / Acıbadem Labmed Health Services A.S.; Codagenix/Serum Institute of India; Indian Immunologicals Ltd/Griffith University	University of Oxford/AstraZeneca; CanSino Biological Inc./Beijing Institute of Biotechnology; Gamaleya Research Institute; ID Pharma; Ankara University; Massachusetts Eye and Ear/Massachusetts General Hospital/AveXis; GeoVax/Bravo Vax; Janssen Pharmaceutical Companies; ReiThera/LEUKOCARE/Univercells; DZIF – German Center for Infection Research/IDT Biologika GmbH; IDIBAPS-Hospital Clinic, Spain; Altimmune; Erciyes University; ImmunityBio, Inc. & NantKwest, Inc.; Greffex; Stabilitech Biopharma Ltd; Valo Therapeutics Ltd; Vaxart; Centro Nacional Biotecnología (CNB-CSIC), Spain; University of Manitoba; University of Georgia/University of Iowa; Bharat Biotech/Thomas Jefferson University; National Research Centre, Egypt; National Center for Genetic Engineering and Biotechnology (BIOTEC)/GPO, Thailand

	Protein Subunit	Replicating Viral Vector	RNA	Virus Like Particles (VLP)
Vaccine Developer/ Manufacturer	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences; Novavax; Kentucky Bioprocessing, Inc; Clover Biopharmaceuticals Inc./GSK/Dynavax; Vaxine Pty Ltd/Medytox; University of Queensland/CSL/Seqirus; Medigen Vaccine Biologics Corporation/NIAID/Dynavax; Mynvax; Izmir Biomedicine and Genome Center; Bogazici University; University of Virginia; Helix Biogen Consult, Ogbomoso & Trinity Immonoefficient Laboratory, Ogbomoso, Oyo State, Nigeria; National Research Centre, Egypt; University of San Martin and CONICET, Argentina; Chulalongkorn University/GPO, Thailand; AdaptVac (PREVENT-nCoV consortium); ExpreS2ion; IMV Inc; WRAIR/USAMRIID; National Institute of Infectious Disease, Japan/Shionogi/UMN Pharma; Osaka University/ BIKEN/ National Institutes of Biomedical Innovation, Japan; University of Pittsburgh; Vaxil Bio; Biological E Ltd; Flow Pharma Inc.; AJ Vaccines; Generex/EpiVax; EpiVax/University of Georgia; EpiVax; Sanofi Pasteur/GSK; Heat Biologics/Univ. Of Miami; FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo; Baylor College of Medicine; iBio/CC-Pharming; Saint-Petersburg scientific research institute of vaccines and serums; Innovax/Xiamen University/GSK; VIDO-InterVac, University of Saskatchewan; OncoGen; MIGAL Galilee Research Institute; LakePharma, Inc.; Baiya Phytopharm/ Chula Vaccine Research Center; Quadram Institute Biosciences; BiOMViS Srl/University of Trento; Lomonosov Moscow State University; University of Alberta; AnyGo Technology; Yisheng Biopharma; Vabiotech; Applied Biotechnology Institute, Inc.; Axon Neuroscience SE; MOGAM Institute for Biomedical Research, GC Pharma; Neovii/Tel Aviv University; Intravacc/Epivax; ImmunoPrecise/LiteVax BV	KU Leuven; Cadila Healthcare Limited; Institute Pasteur/Themis/Univ. of Pittsburg Center for Vaccine Research/Merck; FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo; DZIF – German Center for Infection Research/CanVirex AG; Tonix Pharma/Southern Research; BiOCAD and IEM; FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo; Fundação Oswaldo Cruz and Instituto Buntantan; University of Hong Kong; IAVI/Merck; University of Western Ontario; Aurobindo; FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo; Israel Institute for Biological Research/Weizmann Institute of Science; UW–Madison/FluGen/Bharat Biotech; Intravacc/ Wageningen Bioveterinary Research/Utrecht University; The Lancaster University, UK	Moderna/NIAID; BioNTech/Fosun Pharma/Pfizer; Arcturus/Duke-NUS; Imperial College London; Curevac; People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech; Gennova; Selcuk University; Translate Bio/Sanofi Pasteur; CanSino Biologics/Precision NanoSystems; Fudan University/ Shanghai JiaoTong University/RNACure Biopharma; Centro Nacional Biotecnología (CNB-CSIC), Spain; University of Tokyo/ Daiichi-Sankyo; BIOCAD; RNAimmune, Inc.; FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo; China CDC/Tongji University/Stermina; Chula Vaccine Research Center/University of Pennsylvania; eTheRNA; Greenlight Biosciences; IDIBAPS-Hospital Clinic, Spain	Medicago Inc.; Bezmialem Vakif University; Middle East Technical University; VBI Vaccines Inc.; IrsiCaixa AIDS Research/IRTA-CReSA/Barcelona Supercomputing Centre/Grifols; Mahidol University/ The Government Pharmaceutical Organization (GPO)/Siriraj Hospital; Navarrabiomed, Oncoimmunology group; Saiba GmbH; Imophoron Ltd and Bristol University's Max Planck Centre; Doherty Institute; OSIVAX; ARTES Biotechnology; University of Sao Paulo

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