How New Models of Vaccine Development for COVID-19 Have Helped Address an Epic Public Health Crisis

Abstract

COVID-19 vaccine development and manufacturing have proceeded at a historically unprecedented pace. This speed may be accounted for by (1) the unprecedented scale of resources being devoted to addressing COVID-19; (2) an unusual intensity of cooperation, encompassing the public and private sectors and occurring both within and across national borders; and (3) innovation with respect to both technologies (e.g., new vaccine platforms) and processes (e.g., vaccine clinical trials). In this article, we describe and analyze how resources, cooperation, and innovation have contributed to the accelerated development of COVID-19 vaccines. Similar levels and types of public investment, models of cooperation, and harnessing of innovative processes and technologies could be applied to future epidemics and other global health challenges.

Introduction
Progress towards the successful development and manufacture of effective COVID-19 vaccines has taken place with remarkable speed. In early December 2020, several national regulatory authorities, including the U.S. Food and Drug Administration (FDA), granted emergency or full authorization for a messenger RNA (mRNA) vaccine developed by BioNTech and Pfizer, following review of results from phase III clinical trials. These determinations were quickly followed by FDA emergency use authorization for a second mRNA vaccine developed by Moderna and the U.S. National Institutes of Health (NIH).

Top U.S. public health officials have predicted that hundreds of millions of doses of multiple COVID-19 vaccines will be available to the U.S. population by the second half of 2021 (1). The World Health Organization (WHO) has also suggested that widespread vaccination could take place internationally on a similar timeline (2), although initial delivery has progressed slowly in a number of high-income settings, including the U.S. Considering the potential for further delay in remaining clinical trials, regulatory approval, manufacturing, and distribution, it is perhaps more reasonable to project that substantial global access to COVID-19 vaccination may be achieved sometime between 2022 and 2024. Competition among (wealthy) countries to secure sufficient supplies of vaccine for
their populations with ample room for contingencies may also contribute to slowing global access.

Even so, the rapidity with which both development and, likely, access to COVID-19 vaccines has occurred or is anticipated to occur is entirely without precedent. By comparison, development of the mumps vaccine, which holds the current speed record, took four years from isolation of the mumps virus to licensure in 1967 (3). Indeed, vaccine research and development (R&D), manufacturing, and delivery typically involves a long, deliberate process that takes a decade or more (see Appendix (4)). Achieving widespread coverage with new vaccines can take much longer. Although the WHO has recommended inclusion of pneumococcal vaccine in national immunization programs since 2012, more than half of the global target population still did not receive a full course in 2019 (5).

Several factors have enabled the acceleration of COVID-19 vaccines. Foremost is the scale of resources dedicated to this endeavor. The unusual frequency, nature, and intensity of cooperation among institutions and across borders with respect to COVID-19 in general and vaccination in particular, as well as significant levels of technological and process innovation, have also acted as key drivers by improving the efficiency with which those resources are being put to work.
In this article, we describe and analyze how deployment of substantial financial and human resources, expanded and novel forms of cooperation, and a range of innovations have contributed to the development of COVID-19 vaccines in record time. We conclude with discussion of how approaches taken during the pandemic may be applied to address potential future epidemics and other global health challenges.

Resources

Massive financial and human resources have been dedicated to the global COVID-19 response. As early as July, 2020, more funding had already been poured into COVID-19 vaccine development than into development of any previous vaccine (6). The U.S. government alone has so far committed roughly $13 billion to COVID-19 vaccine developers through its Operation Warp Speed program (7). Many details regarding Operation Warp Speed spending are unclear, in part because the U.S. government has shielded contracts with pharmaceutical companies from public scrutiny (8). However, reporting indicates that roughly $2.5 billion has been allocated to general funding to support vaccine development efforts, with the remainder going to advanced purchase commitments (9). These commitments serve two principal purposes: 1) to guarantee the U.S. government a specified number of vaccine doses and the right to purchase more, and 2) to help finance developers’ scale-up of manufacturing capacity while
clinical trials are ongoing. It also has been reported that the total Operation Warp Speed budget reaches $18 billion, including $6 billion re-allocated from the national COVID-19 stockpile and $1 billion re-allocated from the CDC and originally intended to support state and local health authorities (10). Exhibit 1 summarizes publicly disclosed information about Operation Warp Speed vaccine spending. Other high-income countries are also spending heavily to make COVID-19 vaccination a reality. The United Kingdom has spent more than $4 billion, and the European Union has committed even more. In both settings, funding is divided between financing development and securing vaccine doses. Collectively, wealthy countries accounting for just 13 percent of global population now have rights to more than half of all committed vaccine doses (9).

Some middle-income countries, such as Brazil and Indonesia, have also made advanced purchase arrangements for COVID-19 vaccines. India has announced that it intends to keep roughly half of the 1 billion doses of the Oxford-AstraZeneca vaccine that will be produced by Serum Institute of India (SII) (11). Dedication of significant human resources to the research behind COVID-19 vaccine development has also been key. As of early September 2020, 321 vaccine candidates were in development, with 33 in clinical trials involving 280,000 test subjects across 470
sites in 34 countries (12). Perhaps even more labor has been dedicated to the basic research that undergirds development. One study found that more than 23,000 articles, including more than 10,000 research papers, on COVID-19 had been published in scientific journals by the end of June 2020 and that more than 31,000 documents related to COVID-19 were catalogued on PubMed by mid-July 2020 (13).

**Cooperation**

Under normal circumstances, governmental funders and research institutes, such as the NIH, often collaborate with private vaccine developers on early vaccine R&D. International alliances such as the United Nations Children’s Fund and Gavi, the Vaccine Alliance also coordinate vaccine purchase across many countries. Cooperation therefore frequently plays a key role in vaccine development and distribution, but it has taken place with unusual frequency and force and involved new arrangements of stakeholders during the COVID-19 pandemic. Ongoing forms of cooperation comprise rapid information sharing and private-private, public-private, and public-public partnerships and coalitions, including collective efforts at innovative vaccine finance. Cooperation can improve the efficient use of resources by eliminating unnecessary duplications of effort; it also enables risk sharing and diversification.
Rapid information sharing

The COVID-19 pandemic has coincided with an unprecedented level and pace of information sharing among researchers and policymakers, which has helped fuel rapid vaccine development. Only 42 days after the first COVID-19 patient identified in Wuhan, China developed symptoms, the genetic sequence of SARS-CoV-2 (the virus that causes COVID-19) was deposited in GenBank, a comprehensive genetic sequence database administered by the NIH (14). Within just ten weeks of sequencing, the first vaccine candidate entered a Phase I clinical trial (15).

In general, rapid technical information sharing has exploded during the pandemic. By early May, four popular pre-print servers, medRxiv, arXiv, bioRxiv, and ChemRxiv, had already posted nearly 4,000 COVID-19-related studies spanning disciplines from immunology to biophysics (16). Additionally, among a selection of leading peer-reviewed journals, the average time between submission and publication of COVID-19-related manuscripts has been documented to be half what was standard for those journals prior to the pandemic (17).

While there are certainly benefits to speeding the dissemination of research results that may have relevance to health care or public policy during the pandemic, this acceleration also carries risk, especially when faulty information becomes
amplified through mainstream or social media. For example, a manuscript describing results from a seroprevalence survey in Santa Clara, California came under heavy criticism for failing to acknowledge potential sources of bias and performing questionable statistical analysis (18).

Private-private technical and logistical cooperation COVID-19 vaccine development has been facilitated by private-to-private sharing of vaccine technologies, clinical development capacity, vaccine production techniques and facilities, and experience.

One important and somewhat atypical form of collaboration is the decision of several vaccine developers to license their candidate vaccines to other firms for manufacturing. For example, SII, the world’s largest manufacturer of vaccines by volume, has made deals with both Oxford-AstraZeneca and Novavax to produce 1 billion doses of each candidate vaccine by the end of 2021 (11). If this type of collaboration is adopted more broadly, it could have important implications for future vaccine development and global access.

Multiple vaccine companies are also licensing their proprietary adjuvants to other developers. Adjuvants are substances added to a vaccine to improve its immunogenicity, which can reduce the amount of vaccine required per dose, enabling more doses to be manufactured. Adjuvants can also improve vaccine effectiveness.
in susceptible populations, including older adults. GlaxoSmithKline (GSK), Seqirus, and Dynavax have all committed to making adjuvants contained in their licensed vaccines available for use in novel COVID-19 vaccines developed by other companies (19).

Public-private and public-public collaborations across borders

There has also been an increased amount of public-private collaboration both within and across national borders. A prominent example is the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership. ACTIV is led by the NIH and involves several U.S. governmental agencies, including the Biomedical Advanced Research and Development Authority (BARDA), CDC, FDA, Department of Defense, and Department of Veterans Affairs. It also involves the European Medicines Agency (EMA) and representatives from academia, philanthropic organizations, and pharmaceutical companies (20). The main goal of ACTIV is to develop a collaborative framework for prioritizing vaccine and drug candidates, streamlining clinical trials, coordinating regulatory processes, and leveraging assets. In particular, through ACTIV the NIH has centrally determined the allocation of limited national biomedical resources such as non-human primates and Animal Biosafety Level 3 labs, across the prioritized studies (21).
Additionally, ACTIV’s partners have agreed to contribute their respective clinical trial capacities (e.g., access to clinical trial sites and volunteer networks) irrespective of the vaccine or drug candidate to be studied so as to increase efficiency, prevent the wasteful duplication of trials, and ensure patients’ participation in prioritized clinical trials (20).

The public-private collaboration embodied by ACTIV has been accompanied by intensified coordination among international regulatory authorities (in particular, the FDA, the EMA, and other members of the International Coalition of Medicines Regulatory Agencies). Increased coordination in this domain facilitates the rapid sharing of information on the landscape of medical products for COVID-19 and associated clinical trials, as well as better alignment of regulatory approaches (22).

Collective vaccine finance

COVID-19 vaccine development has been greatly enhanced by financial arrangements under which the public sector cooperates with private vaccine manufacturers to partially absorb the risk of vaccine development. Fast development of multiple COVID-19 vaccines has required substantial government intervention and innovative financial mechanisms. One key challenge is that the private sector is not pre-disposed to fully absorb the risk of investing in a COVID-19 vaccine. While initial outlays for
vaccine R&D may be relatively small, in the tens of millions of dollars, the investment needed to conduct large-scale Phase III trials and then build the facilities to manufacture doses at mass scale ranges from $500 million to $1.5 billion (23). Despite high global demand for a COVID-19 vaccine, developer investment of this nature would have carried substantial risks. The candidate vaccine may not have proven to be safe and efficacious during trials. Following licensure, effectiveness could be undermined by viral mutations. Competition from other vaccines or newly developed therapies may reduce demand. In addition, governments may insist on substantial price concessions.

Faced with this plethora of risks, many vaccine producers might have decided that the potential returns from a COVID-19 vaccine were not worth the investment in the absence of government intervention. This is especially true since vaccine producers often enjoy high patent-protected profit margins on other lines of business and can channel investment away from vaccines. Even if a company judged vaccine development worthwhile, it would have been unlikely to do so speedily. Delaying large-scale investment in vaccine manufacturing until the vaccine’s prospects were more certain would have been the most prudent path. Given the large societal benefits of accelerating the
development of a COVID-19 vaccine, governments have therefore been justified in stepping in to “de-risk” vaccine investment. While the investment was “de-risked” for the vaccine manufacturer, some risks were, in fact, transferred to the public. The government could have paid for vaccine doses that ended up unused if public health measures eliminated the disease, novel treatments reduced its severity, or better vaccines are later developed. However, just as we view insurance a prudent choice even when it is never used, one may view early government investment as insurance against worse outcomes, such as one in which COVID-19 becomes endemic.

One way to de-risk vaccine investment is with direct public funding of manufacturing facilities as done under Operation Warp Speed (7). Expeditious production and delivery of vaccine doses require suitable infrastructure to be in place once a safe and effective vaccine became ready, including building new factories or repurposing existing ones, expanding the supply of specialized materials and resources, such as glass vials and pre-filled syringes, and setting up and testing distributional mechanisms. While direct public funding of manufacturing capacity is not completely novel—for example, the U.S. government previously directly funded capacity for Sanofi Pasteur’s influenza vaccine (24)—this is the first time it had
been done on such a large scale and for vaccines that had not yet been proven effective.

However, complete transfer of risk to the public via direct financing of manufacturing may not be an optimal societal strategy with respect to vaccine investment: Since producers are free to price the vaccine as they see fit once they meet the obligations under their agreement with the government, one might naturally ask if producers should enjoy abnormal profits on a vaccine that received substantial public funding. In addition, requiring producers to put their own capital at risk can help select the most promising projects when the government has less information on how likely a vaccine candidate is to succeed than does the producer.

One way to address these complications is through the use of an advanced purchase or market commitment (APC/AMC) (25,26). An APC is a legally binding contract in which an entity agrees to purchase a quantity of vaccine at a pre-specified price before production if the vaccine meets a given standard. As such, it reduces the risk that a vaccine producer will not find a market; however, the producer retains the risk that it will not produce a vaccine that meets the standard (e.g., a specified level of efficacy). An AMC is similar but is typically run by a non-profit organization (such as Gavi’s AMC to increase take-up of pneumococcal vaccination), on behalf of recipient countries. The
organization retains the option not to purchase the vaccine if demand in the recipient countries fails to materialize. However, in practice, AMCs contain volume guarantees to incentivize vaccine manufacturers’ participation.

As in Operation Warp Speed, the European Commission (EC) has created an APC to secure COVID-19 vaccine doses for its member nations. The initial call for producers resulted in a deal with AstraZeneca to provide 400 million doses and a deal with Sanofi-GSK for 300 million doses (27), although Sanofi-GSK subsequently halted its vaccine trials (28). Over 1.2 billion additional doses have been secured by contracts with Johnson & Johnson, BioNTech-Pfizer, CureVac, and NIH-Moderna. While the final financial terms are confidential, the initial funding is believed to represent a significant portion of the EC’s €2.7 billion ($3.2 billion) Emergency Support Instrument, and total spending is likely to be over $10 billion. Unlike in a traditional APC, Europe provided significant early down-payments on vaccine purchases to further speed development (29).

A key challenge for any global vaccine strategy is defining and achieving an equitable distribution. The main policy innovation to achieve equitable access to a COVID-19 vaccine for low- and middle-income countries is the COVAX-AMC initiative led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, and the WHO. The COVAX-AMC provides producers a guaranteed buyer
for their vaccine if it proves effective. The AMC has committed to buying 300 million doses from AstraZeneca and will be supplied an additional 200 million doses of the same vaccine from SII paid for by the Bill & Melinda Gates Foundation. COVAX ultimately intends to distribute vaccines based on member population and country need, while also maintaining a standing emergency stockpile (30).

While COVAX is a major step toward achieving an equitable distribution of a COVID-19 vaccine, having initially raised $2.1 billion, the initiative has estimated it would need at least $5 billion more by the end of 2021 and potentially up to $18 billion to also fund necessary increases in vaccine manufacturing capacity (31). Recently, this funding gap was partially addressed with a World Bank proposal for up to $12 billion in “fast-track” funding (32). Still, the slow response of wealthy countries to fund the COVAX initiative is regrettable for ethical reasons and because until COVID-19 is controlled throughout the world, all countries will be at risk of at least occasional outbreaks. Additionally, despite the COVAX initiative, the initial distribution of COVID-19 vaccines is likely to be highly unequal, as wealthy countries have already secured rights to well over one billion doses.

Innovation
Like cooperation, technological and process innovation can improve the efficiency with which resources are deployed. The race to develop, manufacture, and deliver a COVID-19 vaccine has involved significant innovation, including with respect to clinical trials and regulatory activity.

**Technological innovation**

A wide range of technical platforms has been used for vaccine development (see Exhibit 2). While some advanced COVID-19 vaccine formulations rely on well-established approaches (e.g., inactivated whole-virus and protein-based vaccines), a number rely on vaccine technologies that had either infrequently or never previously produced an approved vaccine for humans (i.e., the viral vector vaccines and mRNA vaccines). mRNA vaccines instruct the body’s cells to produce a non-infectious version of the viral protein being targeted for a protective immune response without introducing any live, killed, or subunit part of the pathogenic virus. The BioNTech-Pfizer and NIH-Moderna mRNA vaccines were the first vaccines for COVID-19 to receive approval by major regulatory authorities, such as the FDA and the Medicines and Healthcare products Regulatory Agency in the U.K. (33).

In addition to mRNA vaccines, viral vector vaccine candidates for COVID-19 also represent the cutting edge of vaccine R&D.
Such vaccines rely on an attenuated version of a non-target virus to deliver genetic material that will stimulate the vaccinated individual’s cells to make proteins from the target pathogen and thereby provoke an immune response. Viral vector vaccines can either be replicating or non-replicating (i.e., the attenuated virus reproduces in vivo or not).

Four COVID-19 vaccine candidates in Phase III trials rely on the non-replicating viral vector approach using adenovirus, (33). A relatively prevalent pathogen that can cause the common cold. China approved a non-replicating adenoviral vector vaccine against Ebola for emergency use in 2017 (34), and the first official license for human use for a vaccine of this type was granted by the EMA for a different Ebola vaccine in July 2020 (33).

Replicating viral vector vaccines can produce a stronger and more-sustained immune responses than non-replicating or more-traditional vaccines and may permit a single dose vaccine. A replicating viral vector vaccine for Ebola previously received FDA approval. Multiple COVID-19 replicating viral vector vaccines are currently in early development, with the most advanced in phase II trials (33).
In non-pandemic times, the development of a vaccine (from basic research to clinical trials, manufacturing, and distribution) follows a linear sequence of steps (see appendix) (4). Developers use the success of each phase to justify the investment and risk in the next. Several months typically pass between phases to allow for data analysis, publication of findings, and securing approval and financing for the subsequent phase.

The need to speed up the development and delivery of a vaccine has spawned a new paradigm, with many phases executed in parallel rather than sequentially. For example, some developers have combined clinical trial phases or started subsequent clinical phases before confirming the success of previous trials. Normally, vaccines are first tested on a few dozen volunteers in Phase I (dosage and safety trials), then a few hundred in Phase II (expanded safety trials), and thousands in Phase III (large-scale efficacy trials). Combining phases allows developers to test the vaccine on a larger number of people than is customary. For example, BioNTech-Pfizer launched a Phase I/II trial in May to test the safety of their mRNA candidate, with a sample of more than 150 people rather than a few dozen as would normally have happened. In July, they announced the launch of large-scale safety and efficacy Phase II/III trials, with a pool of about 30,000 volunteers, and the plan to further expand it to
44,000 volunteers released in September (35). Exhibit 3 presents other examples of vaccine candidates tested in combined phases. In addition to combining phases, most developers have also conducted parallel clinical trials. The NIH-Moderna mRNA candidate vaccine started Phase III testing on July 27, 2020, after promising results in early clinical trials and while still monitoring subjects and analyzing data from phase I and phase II (35). Russia even took the extreme step of certifying a candidate vaccine for use in select populations well before undertaking a Phase III clinical trial (33).

While moving quickly through COVID-19 vaccine trials could yield significant benefit, it could also prove disastrous if it were to come at the cost of compromised safety. Overlapping early trials implies that large numbers of volunteers are exposed to potential health risks before the results of previous smaller trials have been fully investigated. Likewise, speeding up the regulatory review process implies that there is less time to identify possible side effects.

There is also a risk of important gaps in vaccine trial design. This could take the form of under-representing or omitting key demographic groups, such as ethnic and racial minorities, children, pregnant women, and those who have previously been infected with COVID-19. It could also take the form of failing to adequately track and quantify fundamentally important
endpoints, such as the vaccine’s impacts on severity of disease and transmissibility. Despite the widespread adoption of accelerated development processes, there have been no technical or procedural breakthroughs in assessing short or long-term safety. Potential political pressure to rush the development and regulation process beyond what can be accomplished safely potentially poses additional risk. If an approved vaccine turns out to cause significant and widespread side effects in the general population, it could reinforce existing and foster new vaccine hesitancy with respect to COVID-19 vaccines, and potentially non-COVID-19 vaccines as well.

Conclusion
The full health, economic, and social value of safe, effective, and widespread COVID-19 vaccination would be massive. This suggests that potential returns to acceleration of vaccine R&D, manufacturing, and delivery are correspondingly large. Fortunately, it appears that we may well, in fact, be on track to achieve significant global access to COVID-19 vaccines in record time. This acceleration has largely been fueled by an influx of resources—both financial and human—that is likewise record-setting. Significant levels of cooperation and
innovation, which enable more-efficient use of those resources, have also played a key role.

There may be additional opportunities for innovation that deserve exploration. For example, master protocols, in which multiple vaccine or drug candidates are tested against a single control arm, could further accelerate clinical trials without compromising safety. Innovations to overcome potential delivery impediments, including supply chain challenges and insufficient numbers of health care workers in some regions, would also be welcome.

If widespread COVID-19 vaccination is realized in the coming months and years, the approach undertaken to arrive at that point will offer lessons for how to optimize the development and accessibility of vaccines against other pathogens, under both outbreak and non-outbreak scenarios. Our experiences with COVID-19 may also offer knowledge spillovers to other areas of medicine and public health. For instance, new models of cooperation and innovative finance emerging from the pandemic could be applied to supporting the development of new antimicrobials to counter the mounting threat of antimicrobial resistance.

Efforts undertaken to speedily bring the world safe and effective COVID-19 vaccines hold great promise for protecting human health and economic and social wellbeing. But whether that
promise is realized depends in part on the risks of acceleration and their management. If these can be managed successfully, the global community will owe great thanks to those who have been willing to break the mold when it comes to vaccine development, manufacturing, and delivery.

**References**


4. To access the appendix, click on the Details tab of the article online.


9. Gross A, Bott I. How close is a coronavirus vaccine? Financial Times [Internet]. 2020 Sep 23; Available from: https://www.ft.com/content/e5012891-58da-4a4f-8a05-182adf3ba0e2


https://clinicaltrials.gov/ct2/show/NCT04283461


raised-to-support-equitable-access-to-covid-vaccines-with-additional-us-5-billion-needed-in-2021


Exhibits
Exhibit 1 (table)

Title: Publicly available details of OWS contracts with vaccine developers, as disclosed by Biomedical Advanced Research and Development Authority (BARDA)

Notes: “Total $ for R&D support” refers to money transferred to developers to finance R&D without securing doses for the U.S. government. “Committed doses” refers to the number of doses that the U.S. government has already agreed to purchase (and already paid for in some cases) should they be successfully developed and manufactured. “Total $ for committed doses” refers to the amount of money the U.S. government has agreed to pay for those doses; we reflect the language used by BARDA in its descriptions of the agreements (e.g., “up to $1.2 billion”). “Optional doses” refers to the number of additional doses that the U.S. government has the right to purchase beyond those to which it has already committed; BARDA does not indicate whether prices have been negotiated for optional doses. Double dashes signify that BARDA has not indicated any funding of the given type for the given vaccine developer.

Exhibit 2 (table)

Title: Summary of vaccine technologies used for COVID-19 candidates in clinical trials (updated December 18, 2020)

Notes: This table does not reflect a Phase III trial currently under way to assess whether the bacillus Calmette-Guerin vaccine against tuberculosis, which was developed in the early 1900s, provides partial protection from COVID-19.

**Exhibit 3 (figure)**

Title: COVID-19 vaccine technologies by clinical trial phase

Sources:

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Notes: This figure does not reflect a Phase III trial currently under way to assess whether the bacillus Calmette-Guerin vaccine against tuberculosis, which was developed in the early 1900s, provides partial protection from COVID-19.
Exhibit 1. Publicly available details of OWS contracts with vaccine developers, as disclosed by Biomedical Advanced Research and Development Authority (BARDA)

<table>
<thead>
<tr>
<th>Developer</th>
<th>Total $ for R&amp;D support</th>
<th>Committed doses</th>
<th>Total $ for committed doses</th>
<th>Optional doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson &amp; Johnson</td>
<td>$456 million</td>
<td>100 million</td>
<td>$1 billion</td>
<td>200 million</td>
</tr>
<tr>
<td>NIH and Moderna</td>
<td>$955 million</td>
<td>200 million</td>
<td>Up to $3.2 billion</td>
<td>300 million</td>
</tr>
<tr>
<td>University of Oxford and AstraZeneca</td>
<td>--</td>
<td>300 million</td>
<td>Up to $1.2 billion</td>
<td>Unclear</td>
</tr>
<tr>
<td>BioNTech and Pfizer</td>
<td>--</td>
<td>100 million</td>
<td>$1.95 billion</td>
<td>500 million</td>
</tr>
<tr>
<td>Novavax</td>
<td>--</td>
<td>100 million</td>
<td>$1.6 billion</td>
<td>--</td>
</tr>
<tr>
<td>Sanofi and GSK</td>
<td>$31 million</td>
<td>100 million</td>
<td>$2.04 billion</td>
<td>500 million</td>
</tr>
<tr>
<td>IAVI and Merck</td>
<td>$38 million</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Sources: Higgins-Dunn N. The U.S. has already invested billions in potential coronavirus vaccines. Here’s where the deals stand. CNBC [Internet]. 2020 Aug 14; Available from: https://www.cnbc.com/2020/08/14/the-us-has-already-invested-billions-on-potential-coronavirus-vaccines-heres-where-the-deals-stand.html;


Notes: “Total $ for R&D support” refers to money transferred to developers to finance R&D without securing doses for the U.S. government. “Committed doses” refers to the number of doses that the U.S. government has already agreed to purchase (and already paid for in some cases) should they be successfully developed and manufactured. “Total $ for committed doses” refers to the amount of money the U.S. government has agreed to pay for those doses; we reflect the language used by BARDA in its descriptions of the agreements (e.g., “up to $1.2 billion”). “Optional doses” refers to the number of additional doses that the U.S. government has the right to purchase beyond those to which it has already committed; BARDA does not indicate whether prices have been negotiated for optional doses. Double dashes signify that BARDA has not indicated any funding of the given type for the given vaccine developer.
### Exhibit 2. Summary of vaccine technologies used for COVID-19 candidates in clinical trials (updated December 18, 2020)

<table>
<thead>
<tr>
<th>Vaccine technology/platform</th>
<th># in clinical trials</th>
<th>Most advanced trial stage</th>
<th>Examples of previous use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated virus</td>
<td>8</td>
<td>Licensed in U.A.E. and Bahrain; limited use in China</td>
<td>Influenza, hepatitis A, inactivated polio, and rabies vaccines</td>
</tr>
<tr>
<td>DNA</td>
<td>7</td>
<td>Phase III</td>
<td>Experimental influenza and Zika vaccines</td>
</tr>
<tr>
<td>mRNA</td>
<td>7</td>
<td>Licensed in Bahrain, Canada, and Saudi Arabia; emergency use in several countries, including Singapore, UK, and U.S.</td>
<td>Experimental Middle East respiratory syndrome vaccine</td>
</tr>
<tr>
<td>Type of Vaccine</td>
<td>Phase</td>
<td>Description</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>Replicating viral vector</td>
<td>II</td>
<td>Ebola vaccine (Merck)</td>
<td></td>
</tr>
<tr>
<td>Non-replicating viral vector</td>
<td>III; emergency use in Russia and limited use in China</td>
<td>Ebola vaccine (Johnson &amp; Johnson); experimental HIV vaccine</td>
<td></td>
</tr>
<tr>
<td>Protein subunit</td>
<td>III</td>
<td>Shingles and hepatitis B vaccines</td>
<td></td>
</tr>
<tr>
<td>Virus-like particle</td>
<td>III</td>
<td>Human papillomavirus vaccine</td>
<td></td>
</tr>
<tr>
<td>Live-attenuated</td>
<td>I</td>
<td>Measles, mumps, rubella, varicella, yellow fever, and rotavirus vaccines</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>I</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Total vaccines in clinical trials</td>
<td>57</td>
<td>Phase III; emergency use in Russia and China</td>
<td>NA</td>
</tr>
</tbody>
</table>

Sources:

London School of Hygiene & Tropical Medicine. COVID-19 Vaccine Tracker [Internet]. London School of Hygiene & Tropical Medicine. 2020 [cited 2020 December 18]. Available from: https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/;


Notes: This table does not reflect a Phase III trial currently under way to assess whether the bacillus Calmette-Guerin vaccine against tuberculosis, which was developed in the early 1900s, provides partial protection from COVID-19.