

November 2021

TECHNOLOGY ASSESSMENT

# Vaccine Development

Capabilities and Challenges for Addressing Infectious Diseases



The cover image displays a stylized representation of vaccine research and development in a scientific lab, testing vaccines using artificial intelligence on a computer, manufacturing vaccines and placing them storage containers, an individual receiving vaccination by injection, and financial resources necessary to incentivize the development and manufacturing of vaccines.

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November 2021

## Why GAO did this study

The CARES Act included a provision for GAO to report on its ongoing monitoring and oversight efforts related to the COVID-19 pandemic. This report discusses technologies, approaches, and associated challenges for vaccine (1) research and development, (2) testing, and (3) manufacturing, as well as (4) the economic factors that affect vaccine investment.

GAO conducted literature searches including scholarly articles and government reports relevant to these four areas. GAO interviewed stakeholders and experts with a diverse set of perspectives on the science, administration, and economics of vaccine development. GAO also convened a 3-day meeting of 22 experts with expertise in at least one area related to our four objectives with assistance from the National Academies of Sciences, Engineering, and Medicine. GAO received technical comments on a draft of this report from 1 federal agency and 9 participants at its expert meeting, which it incorporated as appropriate.

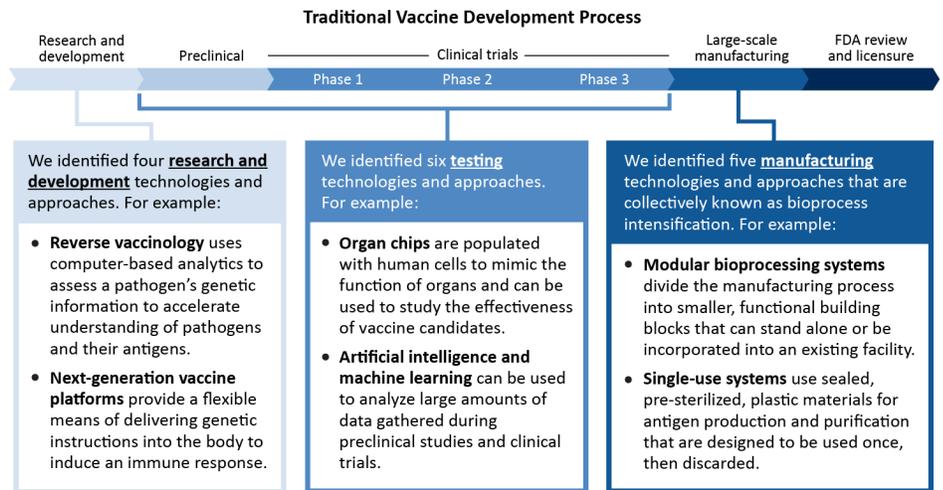
GAO is identifying policy options in this report.

# Vaccine Development

## Capabilities and Challenges for Addressing Infectious Diseases

### What GAO found

Vaccines protect people from disease by preparing the body to respond to an infection. Vaccinations are a key part of individual and community health, but vaccine development remains complex and costly. Innovative technologies and approaches, such as those identified in this report, may enhance the nation's ability to respond to infectious diseases. For example, reverse vaccinology and next-generation platforms—combined with existing research—helped researchers develop some COVID-19 vaccines more quickly and effectively.



Source: GAO analysis. | GAO-22-104371

However, key challenges may hinder the adoption of these innovative technologies and approaches. Some promising technologies face issues and challenges such as inherent technical limitations and high cost. For example, organ chips may facilitate testing, but they are not yet able to replicate many of the complex functions of the human immune system. Similarly, single-use systems may increase the flexibility of vaccine manufacturing facilities, but may require extensive testing to ensure that they do not negatively affect the resulting vaccine. Further, economic challenges may hinder vaccine development. Experts attribute underinvestment in vaccines to market failures (i.e., market interactions that fall short of what would have been socially beneficial). For example, vaccines benefit those who are vaccinated, and, to some degree, those who are not. This additional benefit is not captured in the price, which reduces return on vaccine investment.

GAO identified 9 policy options that may help address challenges hindering the adoption of vaccine development technologies and approaches or economic challenges. These policy options involve possible new actions by policymakers, who may include Congress, federal agencies, state and local governments, academic and research institutions, and industry. See below for details for some of the policy options and relevant opportunities and considerations.

**Selected Policy Options to Address Challenges in Vaccine Development**

	<b>Opportunities</b>	<b>Considerations</b>
<p><b>Prioritize infectious disease pathogens</b> (report page 21)                      Policymakers could collaborate across sectors (e.g., government, academia, researchers, industry, and nonprofit organizations) to prioritize infectious disease pathogens with pandemic potential for vaccine R&amp;D.                      For example, policymakers could develop a working group to prioritize pathogens with pandemic potential and work more closely with international organizations to prioritize vaccine development as well as develop monoclonal antibodies.</p>	<ul style="list-style-type: none"> <li>• Prioritizing pathogens with pandemic potential could improve strategic vaccine R&amp;D decision-making and help focus resources on developing and adopting key technologies and approaches that most effectively address those pathogens.</li> <li>• Appropriately matching the technologies and approaches to the prioritized potential pandemic pathogens then leveraging technologies may help address certain technical limitations and cost.</li> <li>• With greater leadership and strategic partnerships, policymakers could more quickly address threats to the U.S. population.</li> </ul>	<ul style="list-style-type: none"> <li>• As new threats are identified, priorities may change, which may cause uncertainty for vaccine developers.</li> <li>• Policymakers may have different priorities based on their respective missions.</li> <li>• There may be disagreements as to which key technologies should be prioritized and used, resulting in the need for policymakers to weigh the potential advantages and disadvantages associated with various options.</li> </ul>
<p><b>Improve preparedness</b> (report page 21)                      Policymakers could provide support for public-private partnerships to strategically address potential pandemic pathogens identified as priorities. These partnerships could, for example, develop and test vaccine candidates that may provide protection from pathogens with pandemic potential.</p>	<ul style="list-style-type: none"> <li>• This early development could provide a coordinated foundation that can be mobilized in an emergency. Such an approach could speed vaccine development as well as potentially reduce risk for vaccine researchers and developers concerning questions of safety, efficacy, and manufacturability.</li> </ul>	<ul style="list-style-type: none"> <li>• The lack of certainty of the commercial market and government funding for vaccines against pathogens with pandemic potential may be too risky for the private sector to undertake.</li> </ul>
<p><b>Further support development of data standards</b> (report page 32)                      Policymakers could further support coordinated efforts to obtain the views of all stakeholders and to develop standards for health data and their use in clinical trials.</p>	<ul style="list-style-type: none"> <li>• Integrating researchers’ needs into the standards development process could better ensure the necessary data are available.</li> <li>• Access to high-quality data in a standardized format may allow streamlined patient recruitment for clinical trials.</li> </ul>	<ul style="list-style-type: none"> <li>• Expanding access to patient health data requires attention to ensure privacy.</li> <li>• Developing and implementing standardized data formats and IT infrastructure is time-consuming and costly.</li> </ul>
<p><b>Improve preparedness</b> (report page 41)                      Policymakers could provide support for public/private partnerships to strategically develop manufacturing capacity to respond to surge requirements. To maintain this capacity, partnerships could manufacture prototype vaccine candidates against high-priority pathogens.</p>	<ul style="list-style-type: none"> <li>• Manufacturing, testing, and stockpiling vaccines could be mobilized in an emergency and more rapidly mitigate future pandemics.</li> <li>• By leveraging strategic partnerships, policymakers could take steps to increase the availability of vaccines to more quickly address threats to the U.S. population.</li> </ul>	<ul style="list-style-type: none"> <li>• May require new resources or reallocation of resources from other efforts.</li> <li>• There may be a risk that the vaccines manufactured, tested, and stockpiled against prioritized pathogen classes miss certain pandemic pathogens.</li> <li>• The stockpiled vaccines would need to be regularly replenished prior to expiration.</li> </ul>
<p><b>Evaluate factors that inhibit vaccine investment and mechanisms to increase it</b> (report page 54)                      Policymakers could collaborate across sectors, such as government, academia, and industry, to conduct a systematic evaluation of factors that inhibit developers from investing in new vaccines.</p>	<ul style="list-style-type: none"> <li>• A clear understanding of the range of factors discouraging vaccine investment would provide the basis for effectively addressing those factors.</li> </ul>	<ul style="list-style-type: none"> <li>• Collaboration between policymakers and other stakeholders to obtain all relevant viewpoints can be time-consuming and it may be hard to reach a consensus.</li> </ul>

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## Abbreviations

AI	artificial intelligence
BARDA	Biomedical Advanced Research and Development Authority
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 2019
DOD	Department of Defense
EHR	electronic health record
EUA	emergency use authorization
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
MERS	middle east respiratory syndrome
ML	machine learning
mRNA	messenger RNA
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
R&D	research and development
SARS	severe acute respiratory syndrome
WHO	World Health Organization



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## Introduction

November 16, 2021

### Congressional Committees

Vaccinations are an important tool for individual and public health, and have saved millions of lives. For example, between 1900 and 1980, smallpox killed approximately 300 million people and disfigured millions more. However, by 1980, a successful vaccination campaign eliminated smallpox worldwide. Similarly, in 1988, at the onset of a global campaign to end polio, there were 350,000 polio cases worldwide. According to the World Health Organization (WHO), the number of polio cases has since declined by over 99 percent worldwide.

Infectious diseases carry a high price tag for society. According to the World Bank, the economic losses from six major outbreaks of highly fatal infectious diseases that occurred between 1997 and 2009 amounted to at least \$80 billion globally.<sup>1</sup> According to the National Foundation for Infectious Diseases, in the U.S., an average influenza illness can last up to 15 days, typically resulting in 5 or 6 missed work or school days. Adults who contract hepatitis A lose an average of one month of work. Further, when people are not vaccinated, they may be vulnerable to serious infections, such as human papillomavirus and hepatitis B (both can cause cancer), which have significant personal and economic burdens.

Providing the public with safe and effective vaccines is also crucial to mitigating global pandemics. The Coronavirus Disease 2019 (COVID-19) pandemic has highlighted the devastating impact new infectious diseases can have. As of November 1, 2021, the Centers for Disease Control and Prevention (CDC) reported that over 745,000 people in the U.S. had died of COVID-19. An October 2020 study estimated the total economic cost of the at more than \$16 trillion, or approximately 90 percent of the annual U.S. gross domestic product.<sup>2</sup> In December 2020, the U.S. took an important step to protect the public against COVID-19, as the first COVID-19 vaccines—developed in a shorter time than any previous vaccine—were authorized for

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<sup>1</sup>The infectious diseases included in this study were Nipah Virus (Malaysia), West Nile Fever (U.S.), severe acute respiratory syndrome (Asia, Canada, other), highly pathogenic avian Influenza (Asia, Europe), bovine spongiform encephalopathy (U.S., U.K.), Rift Valley Fever (Tanzania, Kenya, Somalia). See World Bank People, Pathogens and our Planet: The Economics of One Health. 2012, Washington, DC. <https://openknowledge.worldbank.org/handle/10986/11892>.

<sup>2</sup>D.M. Cutler and L. Summers “The COVID-19 Pandemic and the \$16 Trillion Virus,” *Journal of the American Medical Association*, Oct. 20, 2020.

emergency use and administered.<sup>3</sup> As of November 2021, three COVID-19 vaccines were available in the United States. One vaccine was licensed by the Food and Drug Administration (FDA) for individuals 16 and older, and was also available for individuals aged 5-15 years under an emergency use authorization (EUA).<sup>4</sup> Since implementation of the COVID-19 vaccine program in December of 2020, the number of new daily cases has declined.<sup>5</sup> For example, the number of COVID-19 cases in the U.S. reached a high of over 290,000 new daily cases on January 8, 2021, but declined to about 75,000 new daily cases as of November 2, 2021.<sup>6</sup>

While the National Institutes of Health (NIH) conducts and supports research that contributes to relevant technological advances, vaccine development overall continues to be a difficult, complex, and costly endeavor, and from an investment standpoint remains highly risky for those who pursue it. Economists we spoke to stated that the benefits that vaccines provide are not necessarily commensurate with the return on investment from developing or manufacturing them and vaccine development from discovery to licensure can cost billions of dollars and can take over 10 years to complete.<sup>7</sup> Vaccine developers face numerous technical challenges related to the biological complexity of some infectious diseases and the maturity of new vaccine technologies. Other challenges include long development time frames, high rates of clinical trial failure, and the lack of incentives to invest in vaccines.

Given the public health consequences of infectious disease, policymakers have a vital interest in developing and maintaining modern, flexible, rapid, and robust vaccine development and manufacturing capabilities.<sup>8</sup> These capabilities will allow for better response to endemic levels of infectious disease, as well as better preparation for potential future epidemics and

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<sup>3</sup>The Secretary of Health and Human Services (HHS) may declare that circumstances, prescribed by statute, justify the emergency use of certain medical products, such as vaccines. Once a declaration of an emergency has been made, the Food and Drug Administration (FDA) may temporarily allow use of unlicensed vaccines through an emergency use authorization (EUA). For FDA to issue an EUA for a vaccine, it must be reasonable to believe that the vaccine may be effective and that the known and potential benefits of the vaccine outweigh the known and potential risks, among other statutory criteria. See 21 U.S.C. § 360bbb-3. See also HHS, FDA, Center for Biologics Evaluation and Research, *Emergency Use Authorization for Vaccines to Prevent COVID-19, Guidance for Industry*, (Washington, D.C.: May 2021).

<sup>4</sup>FDA licenses biological products, such as vaccines, through review and approval of a biologics license application. See 42 U.S.C. § 262. FDA guidance indicates that licensure is the goal for COVID-19 vaccines, including those that first receive an EUA.

<sup>5</sup>COVID-19 vaccine implementation involves the prioritization, allocation, distribution, and administration of vaccine doses.

<sup>6</sup>For more information on the accelerated COVID-19 vaccine development process, see GAO, *COVID-19: Efforts to Increase Vaccine Availability and Perspectives on Initial Implementation*, GAO-21-443, (Washington, D.C.: April 14, 2021), GAO, *Operation Warp Speed: Accelerated COVID-19 Vaccine Development Status and Efforts to Address Manufacturing Challenges*, GAO-21-319, (Washington, D.C.: Feb. 11, 2021), and GAO, *COVID-19: Federal Efforts Accelerate Vaccine and Therapeutic Development, but More Transparency Needed on Emergency Use Authorizations*, GAO-21-207 (Washington, D.C.: Nov. 17, 2020). GAO has also produced an interactive dashboard that integrates multiple data sources to visualize the status of vaccine development, which may be found at <https://ows.gaoinnovations.gov/>

<sup>7</sup>D. Gouglas et al., "Estimating the Cost of Vaccine Development Against Epidemic Infectious Diseases: a Cost Minimisation Study." *The Lancet Global Health*, vol. 6, no. 12 (2018): pp. e1386-e1396.

<sup>8</sup>Policymakers is a broad term including, for example, Congress, federal agencies, state and local governments, academic and research institutions, and industry.

pandemics.<sup>9</sup> This urgent need comes at a time marked by rapid growth in basic scientific understanding—in areas such as genomics and structural biology that are supporting a new era in vaccine development—as well as ongoing challenges.

The CARES Act includes a provision for GAO to report on its ongoing monitoring and oversight efforts related to the COVID-19 pandemic.<sup>10</sup> This technology assessment is part of our body of work in response to the CARES Act and describes various technologies and approaches applicable to developing vaccines for infectious diseases. Specifically, in this technology assessment, we describe

- technologies and approaches for vaccine research and development (R&D) and challenges that affect their use,
- technologies and approaches for vaccine testing and challenges that affect their use,
- technologies and approaches for vaccine manufacturing and challenges that affect their use, and
- economic factors that affect vaccine investment and preparedness for future pandemics.

To address all of our objectives, we conducted literature searches including scholarly articles and government reports describing current and emerging technologies and approaches for vaccine R&D, testing, and manufacturing.<sup>11</sup> We used the results of our literature review to address our objectives as well as identify experts to interview and invite to participate in our expert meeting. Additionally, we interviewed stakeholders and experts with a diverse set of perspectives on the science, administration, and economics of vaccine development. To address all of our objectives, we held an expert meeting from January 25-28, 2021. This meeting was held in collaboration with the National Academies of Sciences, Engineering, and Medicine, and was divided into six sessions on technologies and approaches for vaccine: (1) research and development; (2) manufacturing, (3) preclinical and clinical trials, (4) pathogen scenarios, (5) economics factors, and (6) lessons learned.

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<sup>9</sup>Endemic refers to the constant presence or usual prevalence of disease in a population within a geographic area. An epidemic refers to an increase, often sudden, in the number of cases of a disease above what is normally expected in a population and area. A pandemic refers to an epidemic that has spread over several countries or continents, usually affecting a large number of people.

<sup>10</sup>Pub. L. No. 116-136, § 19010, 134 Stat. 281, 579-81 (2020). We regularly issue government-wide reports on the federal response to the COVID-19 pandemic. For our 8<sup>th</sup> comprehensive report on the ongoing federal pandemic response, see GAO, *COVID-19: Additional Actions Needed to Improve Accountability and Program Effectiveness of Federal Response*, GAO-22-105051, (Washington, D.C.: Oct. 27, 2021). Our next government-wide report will be issued in January 2022 and can be found on GAO's website at <https://www.gao.gov/coronavirus>.

<sup>11</sup>For purposes of this report, vaccine testing refers to preclinical studies, clinical trials, and post-marketing surveillance studies.

Based on the information we obtained, we developed a series of policy options intended to represent possible options that policymakers can take to address a policy objective. Consistent with our quality assurance framework, we provided the relevant agencies and experts with a draft of our report and solicited their feedback, which we incorporated as appropriate. See appendix I for additional information on our scope and methodology.

We conducted our work from June 2020 through November 2021 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

# 1 Background

## 1.1 How vaccines work

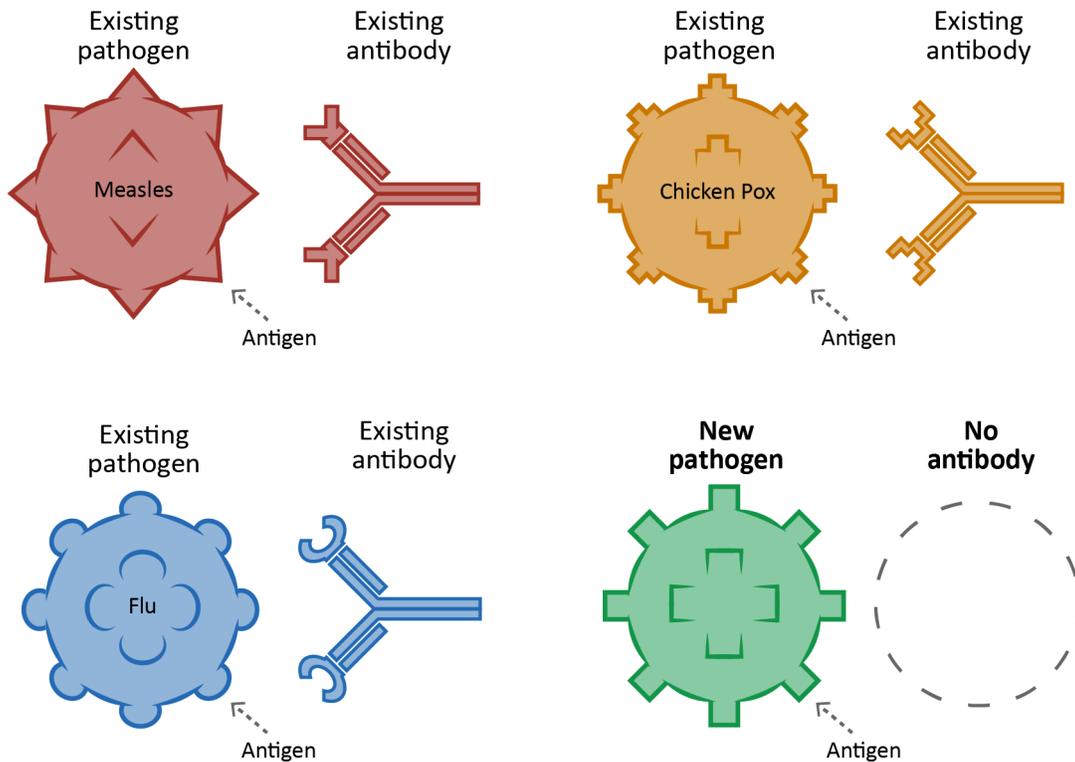
Vaccines protect people from disease by triggering the immune system to produce antibodies that will fight a pathogen attacking the body. A pathogen is a bacterium, virus, or other microorganism that can cause disease. Preparing the immune system through vaccination allows the body to respond more quickly if that pathogen infects the individual in the future.

During an infection, the immune system responds to specific parts of a pathogen called antigens by producing antibodies—proteins that help bind to and neutralize specific pathogens—to fight the pathogen

and in some cases prevent future infections (see fig. 1). The immune system also produces specific cells—such as T-lymphocytes—that assist in neutralizing pathogens in a process known as cell-mediated immunity. When the human body is exposed to an antigen for the first time, it takes time for the immune system to respond and produce antibodies specific to that antigen. During that period of time, the individual is susceptible to becoming ill from the disease caused by the pathogen. Once antigen-specific antibodies are produced, they work with the rest of the immune system to destroy the pathogen.

Vaccines mimic this natural process by introducing antigens without necessarily introducing the disease-causing pathogen

**Figure 1: How antibodies fight invading pathogens**



Source: World Health Organization (WHO), <https://www.who.int/news-room/feature-stories/detail/how-do-vaccines-work> (accessed June 30, 2021). | GAO-22-104371

itself; for example, vaccines can use a weakened or inactive pathogen, a microorganism that is closely related to the pathogen but does not cause disease in humans, or a molecule derived from the pathogen.<sup>12</sup> Vaccines may include a variety of ingredients such as stabilizers, adjuvants, and preservatives to enhance the effectiveness of the vaccine or offer other benefits.<sup>13</sup>

Once an immune response has been generated, if the person is exposed later to the pathogen, their immune system will ‘remember’ seeing that pathogen and respond more quickly, increasing their chances of fighting off the infection.<sup>14</sup> Additionally, vaccines that protect against one pathogen may also protect against similar pathogens. Vaccines may also reduce the spread of infectious disease, which can convey some level of protection to those who are not vaccinated. For example, the bacille Calmette–Guérin vaccine, which contains weakened *Mycobacterium bovis*—a bacterium that causes tuberculosis in cattle—is used to protect humans from *Mycobacterium tuberculosis*—a bacterium that causes tuberculosis in humans. Further, this vaccine may also provide some protection

against *Mycobacterium leprae*—a bacterium that causes leprosy in humans.

## 1.2 Vaccine development

The traditional process for developing a new vaccine is well established and tends to be sequential (see fig. 2), although stages sometimes overlap.<sup>15</sup> The purpose of this sequential approach is, in part, to reduce financial risk because each stage is costly—with later stages being especially costly—and each stage improves the understanding of whether the next stage might be successful. However, one expert told us that this is not guaranteed. At any stage, the process can be terminated for a variety of reasons, including detection of adverse events, such as serious side effects or if the evidence suggests that the vaccine is unlikely to be protective.

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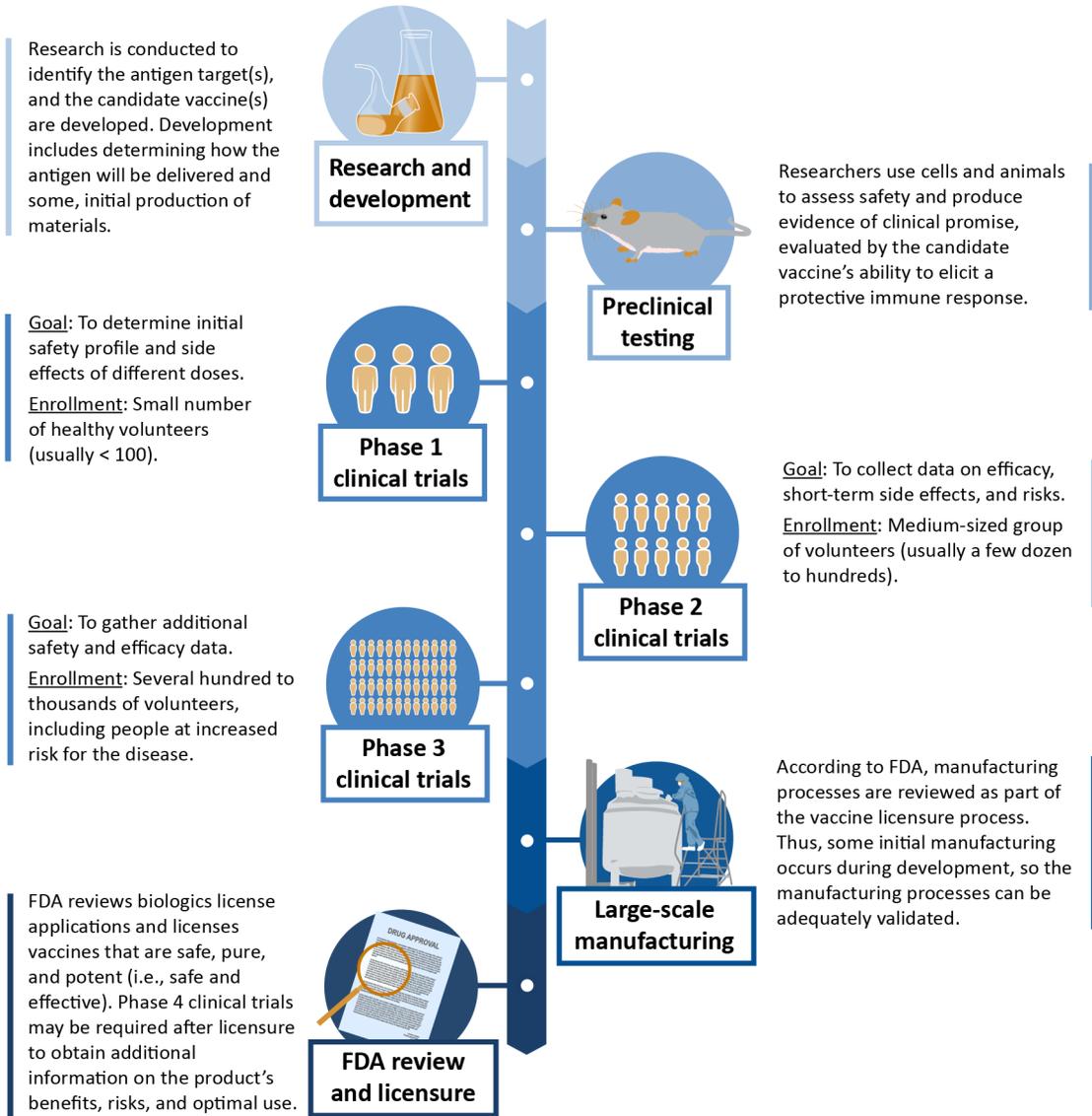
<sup>12</sup>For example, the smallpox vaccine uses a related poxvirus, the vaccinia virus, which is unlikely to cause significant disease in healthy human recipients, but elicits an immune response that is protective for smallpox.

<sup>13</sup>Stabilizers are substances such as amino acids and other substances that help the antigen maintain its effectiveness during storage. Adjuvants are compounds such as aluminum salts that help to enhance the immune response. Preservatives are chemical substances that help to protect against bacterial and fungal growth during storage. (<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/common-ingredients-us-licensed-vaccines>).

<sup>14</sup>Vaccine effectiveness varies for each vaccine. For example, according to CDC, the effectiveness of seasonal influenza vaccines ranges from between 40 percent to 60 percent during seasons when influenza vaccine viruses are similar to circulating influenza viruses, while a two-dose course of the measles, mumps, and rubella vaccine is 97 percent effective at preventing measles.

<sup>15</sup>We have previously reported on the traditional vaccine development timeline compared to a potential timeline for COVID-19 vaccine development. See [GAO-21-319](#).

**Figure 2: Traditional vaccine development process**



Source: GAO analysis of information from the Food and Drug Administration (FDA) and literature. | GAO-22-104371

Note: The steps shown in the timeline are not drawn to scale, and the specific development steps for a given vaccine may vary. For example, the federal government accelerated this process for the development of a COVID-19 vaccine under the HHS-DOD COVID-19 Countermeasures Acceleration Group (formerly known as Operation Warp Speed) by overlapping certain phases to speed up the process so the vaccines could be used as quickly as possible to control the pandemic. No trial phases were skipped.

In this report, we use the term “efficacy” to refer to the results of adequate and controlled clinical trial studies that evaluate clinical disease endpoints, and “effectiveness” to refer to the results of studies carried out under field conditions. For regulatory purposes, FDA determines whether a vaccine is safe and effective, and effectiveness is generally based on the results of adequate and well controlled studies evaluating a clinical disease endpoint (efficacy studies) or a well-accepted immune endpoint (effectiveness studies).

Chapters 2 through 4 of this report discuss technologies and approaches to enhance overall response to endemic infectious diseases, as well as improve capabilities to respond to potential future epidemics or pandemics. Specifically, chapter 2 discusses the vaccine R&D stage; chapter 3 focuses on vaccine testing, including preclinical testing, clinical trials, and post-marketing surveillance; and chapter 4 discusses vaccine manufacturing. Chapter 5 of this

report discusses economic challenges that may result in fewer vaccines being developed and tools to incentivize additional vaccine investment to enhance overall response to endemic infectious disease, as well as improve capabilities to respond to potential future epidemics and pandemics.

## 2 Technologies and Approaches for Vaccine R&D

Technologies and approaches for vaccine R&D may help researchers, developers, or other scientists better identify and characterize pathogens and their antigens—the components of the pathogen that stimulate an immune response—and determine how the human immune system responds to pathogens. This improved understanding may also result in more efficient generation of safe and effective vaccines and other biological products, such as monoclonal antibodies.<sup>16</sup> However, the use of some technologies may be affected by their inherent technical limitations, complexity, and high cost. Further, while policymakers—which include Congress, federal agencies, state and local governments, academic and research institutions, and industry—have supported vaccine R&D for many infectious diseases, it is not clear the extent to which they have prioritized specific potential pandemic pathogens for vaccine R&D.<sup>17</sup> This lack of clarity raises questions about whether vaccine R&D efforts, and the technologies needed to support those efforts, enhance the capabilities to best respond to endemic levels of infectious disease and potential future epidemics and pandemics.

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<sup>16</sup>Biological products, which include a wide range of products—including vaccines, blood and blood components, allergenics, somatic cells, gene therapy, and tissues, among other things—are derived from living sources such as humans, animals, and microorganisms. See 42 U.S.C. § 262(i)(1) and 21 C.F.R. § 600.3(h) (2020).

<sup>17</sup>NIH conducts and supports basic, translational, and applied clinical research that contributes to technological advances relevant for vaccine development. For example, NIH officials noted the National Institute of Allergy and Infectious Diseases' (NIAID) role in funding research on SARS and Middle East

### 2.1 Factors Affecting Vaccine R&D

Key factors in conducting vaccine R&D are:

- Identifying and characterizing a pathogen's key antigens and the immune system response
- Applying knowledge about antigens and immune responses to rapidly develop vaccines or other biological products that safely and effectively stimulate or complement an immune response
- Considering the various routes of delivery, including alternative routes such as dermal or oral, that may help maximize vaccination rates

Identifying antigens that stimulate a protective immune response has, traditionally, been a slow process done largely through trial-and-error testing. Any given pathogen may have thousands of potential antigens, and the human immune system includes many different types of cells with different functions, not all of which are fully understood. To identify the antigens that most effectively stimulate a protective response in the human immune system, researchers typically select and test potential

Respiratory Syndrome (MERS) contributed to the successful development of vaccines for COVID-19. However, we note that no commercial vaccines for SARS or MERS exist. This was partly attributed to lack of continued investments in a vaccine for SARS, for which cases ceased to be reported, and for MERS, which resulted in relatively few and geographically isolated cases. One expert who had developed a SARS vaccine candidate stated that had that vaccine been able to proceed through phase 1 clinical trials and stockpiled, it could have been beneficial for COVID-19 and accelerated vaccine development.

antigens one or a few at a time. Researchers then run laboratory tests or conduct animal studies to see if any of the antigens they selected produces a protective immune response. (See text box for one example of how antigens were identified.)

It is also difficult to quickly develop vaccines that safely and effectively stimulate an immune response. There are many reasons for this, but two key factors are the time needed to produce antigens and a lack of adaptability. First, traditional vaccine development often requires the growth of pathogens or the use of other cells, such as bacteria, yeast, or insect cells, containing the antigen(s) of interest from the pathogen. Viral pathogens can be grown in eggs or other cells—known as cell cultures. These methods can take months to years to develop. Second, traditional methods of vaccine development may be not highly adaptable for multiple pathogens or diverse antigens. This may limit the ability to quickly develop vaccines when new pathogens emerge or change a vaccine when variants arise.<sup>18</sup>

Finally, administering vaccines by injection using a needle and syringe—the traditional method of delivering vaccines—may affect, for example, some individuals’ willingness to get a vaccination due to a fear of needles. Additionally, the need for trained personnel and the costs and potential scarcity of vaccination supplies (e.g., vials, syringes, and needles), particularly during pandemics, can make administration of vaccines using traditional injections difficult.

#### Coronavirus research

In the case of COVID-19, identifying and characterizing the spike protein antigen was the result of decades of previous research dating back to human coronavirus research begun in the 1960s, the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003-2005, and the Middle Eastern Respiratory Syndrome (MERS) outbreak of 2012. If earlier research on SARS and MERS had not been funded, development of a COVID-19 vaccine may have taken significantly longer.

Source: GAO analysis of information from literature and an expert meeting. | GAO-22-104371

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<sup>18</sup> A variant is a new form of the same pathogen that arises from distinct changes—also known as mutations—in the genetic sequence of the pathogen.

## 2.2 Technologies and approaches for vaccine R&D

Drawing on information from experts, stakeholders, and related literature, we

identified four technologies and approaches that may improve vaccine R&D (see table 1). Appendix II provides additional information on these technologies and approaches.

**Table 1: Selected technologies and approaches for vaccine research and development (R&D)**

Name	Description
<b>Omics</b>	Omics refers to the combined analyses of DNA (genomics and epigenomics), RNA (transcriptomics), proteins (proteomics), other small molecules (metabolomics), and other biological components. In vaccine R&D, omics is meant to improve the understanding of pathogens and host immune responses.
<b>Reverse vaccinology</b>	Reverse vaccinology uses computer-based analytics to assess a pathogen’s genetic code and identify potential antigens. Reverse vaccinology allows researchers to identify potential vaccine antigen candidates without the need to grow the pathogens and develop vaccines that were previously difficult or impossible to make.
<b>Next-generation vaccine platforms</b>	Next-generation vaccine platforms incorporate the genetic information that codes for a pathogen’s antigen into a delivery vehicle. A delivery vehicle can be another virus (viral vector), a microparticle, or a lipid nanoparticle. The delivery vehicle protects the genetic information until it is administered into an individual, where the immune response is triggered. The platform may also be able to be used in a plug-and-play fashion to pair a delivery vehicle with different genetic sequences to create new or updated vaccines. Vaccine platforms may have uniform, predictable characteristics, such as safety effects; however, each antigen in a specific platform will have different immune response characteristics. <sup>a</sup>
<b>Routes of vaccination</b>	Traditional vaccinations are delivered by injection either under the skin (subcutaneous) or into muscle (intramuscular). The identification and use of nontraditional vaccine delivery routes, such as dermal (skin) and mucosal (oral, nasal) may offer the potential for better immune responses, increased public acceptance, and lower dosages.

Source: GAO. | GAO-22-104371

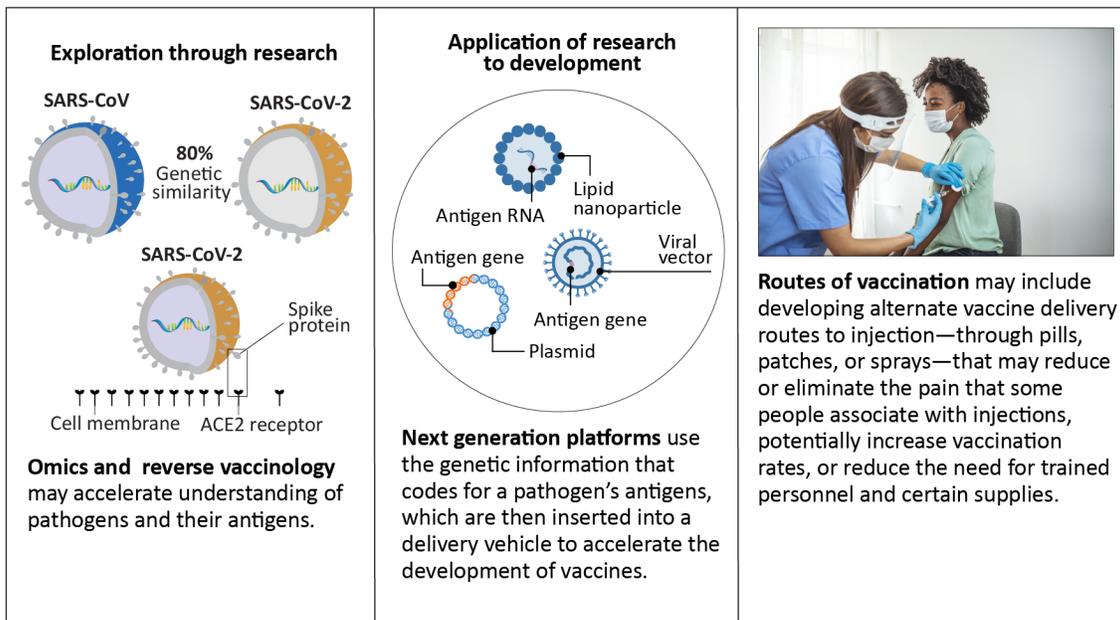
<sup>a</sup>According to National Institutes of Health (NIH), vaccine platform technologies are approaches, delivery systems, and other tools that serve as the basis for delivering those vaccine antigen designs and for the development of candidate vaccines. Vaccine prototype design is the research and development that results in a candidate antigen design as the basis of a vaccine.

The technologies and approaches we identified can be applied at different stages of vaccine R&D. For example, in early exploration and research, omics and reverse vaccinology can help researchers to more rapidly identify antigens and how they stimulate an immune response. For later stages of vaccine R&D, genetic code for the identified antigens can be quickly incorporated into delivery vehicles, such as lipid nanoparticles or viral vectors, accelerating vaccine testing (see fig. 3).

biological molecules. Then, researchers can apply computer simulations to predict more quickly which of the potential antigens may stimulate an immune response and which modifications to the antigens may enhance the immune response. As a result, researchers can more quickly begin testing those antigens that are most likely to work. (See text box for an example of how reverse vaccinology has been used.)

Omics and reverse vaccinology aid in the early exploration process by helping researchers to more quickly identify antigens that stimulate a protective immune response by analyzing the pathogen’s DNA, RNA, proteins, or other

**Figure 3: Selected application of technologies and approaches used during vaccine research and development**



Source: GAO analysis of scientific literature and narstudio/Dragana Gordic/stock.adobe.com. | GAO-22-104371

### Reverse vaccinology and the COVID-19 vaccine

Researchers used reverse vaccinology to accelerate development of some COVID-19 vaccines. When the genetic code of SARS-CoV-2—the virus that causes COVID-19—became available, researchers quickly identified it as a coronavirus similar to the Severe Acute Respiratory Syndrome (SARS) coronavirus. According to the National Institutes of Health (NIH), this enabled researchers to use information gained from prior National Institute of Allergy and Infectious Diseases (NIAID)-funded studies, among others, that used reverse vaccinology and protein structure analysis to characterize the SARS and Middle East Respiratory Syndrome (MERS) spike protein antigens and their human cell receptors. This then helped researchers more quickly identify, assess, and stabilize the spike protein from SARS-CoV-2, which, in turn, allowed for the quick development of potential COVID-19 messenger RNA (mRNA) vaccine candidates, according to NIH. Researchers were able to test mRNA vaccines in a phase 1 clinical trial within 90 days of the SARS-CoV-2 genetic code release. In comparison, the vaccine candidates for MERS and SARS reached clinical trials within about 22 months and 25 months, respectively, after their outbreaks. Dengue, Chikungunya, and Zika vaccine candidates took even longer to reach clinical trials: approximately 52 years, 19 years, and 9 years, respectively, after declaration of major outbreaks. According to Food and Drug Administration (FDA) officials, other differences, including the nature of the pathogens and funding levels, also contributed to the extended development timeframes.

Source: GAO analysis of literature. | GAO-22-104371

Omics can also help researchers characterize the human immune system by allowing researchers to understand which cells provide protection. Omics analysis of the immune system may also enable researchers to predict how individuals may react to vaccines and could allow for tailored vaccines for certain populations.<sup>19</sup>

Next-generation vaccine platforms, such as nucleic acid (e.g., mRNA and DNA) and viral vector platforms, also aid in the development

of a vaccine. Specifically, next-generation platforms can help speed development, particularly when new pathogens emerge, because they rely on the pathogen’s genetic information that codes for antigens. This eliminates the need to grow the pathogen or purify antigens. These platforms are also highly adaptable to multiple pathogens, allowing the development of many different vaccines to address a diverse range of pathogens on a single platform. They also have the potential to be used to develop universal vaccines which protect against multiple pathogens from the same or closely related families. However, next-generation platforms may not be practical for certain pathogens or developing countries, according to one expert we spoke to.

Three nontraditional routes of vaccination—dermal, nasal, and oral—are an important consideration in vaccine development. Using nontraditional routes of vaccination can reduce or eliminate the pain that some people associate with injections, potentially increasing vaccination rates or reducing the need for trained personnel and certain supplies.

- **Dermal delivery.** Delivering vaccines through the skin can produce strong immune responses at much lower doses than intramuscular and subcutaneous vaccines, making it a good route for vaccination. Microneedles, which can be

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<sup>19</sup>For example, researchers used omics analysis to characterize the differences in the immune system to the hepatitis B vaccine in two groups of older adults, one that quickly produces high levels of antibodies and another that does not produce any response. The results of these studies may enable researchers to better predict vaccination outcomes—whether a strong, weak, or no immune response occurs—in individuals and help researchers increase vaccine effectiveness.

nearly pain-free, are small structures designed to pierce the skin and deliver vaccines in the epidermis or dermis layers.<sup>20</sup> FDA has licensed one influenza vaccine that uses dermal delivery.

- **Nasal delivery.** Nasal vaccines can induce immunity even at distant sites of the body. The antigens are taken up by cells in the nasal cavity, stimulating a potent antibody in the respiratory tract that prevents the pathogen from entering the body. The antigens also stimulate the body's overall immune response, which may increase the general effectiveness of the vaccine. There are FDA-licensed nasal vaccines for seasonal influenza; however, in the past, one was less effective than an injected vaccine.<sup>21</sup>
- **Oral delivery.** The intestine contains 70 to 80 percent of all antibody-producing cells in the body. Oral vaccination—delivered in a pill or liquid form—can induce a broad protective immune response in the body (including the intestine), which can be difficult to achieve using injections with needles and syringes. However, oral vaccines must be formulated to protect against degradation in the gastrointestinal tract, while still stimulating an effective immune response. Examples of oral vaccines in use

today include those for polio, rotavirus, and cholera.<sup>22</sup>

Additionally, experts we spoke with emphasized that monoclonal antibodies are emerging as a potential approach to preventing infections. Monoclonal antibodies are laboratory-produced antibodies that act to mimic the immune system's ability to fight off pathogens. They are not vaccines and have traditionally been used as treatments for individuals that are already infected. However, many of the same types of technologies—for example, omics and delivery platforms—used for vaccine development could also be used for monoclonal antibodies. Unlike vaccines, which can stimulate an individual's immune system to produce protective antibodies for years, monoclonal antibodies may provide shorter protection against infectious diseases, usually for weeks to months. If able to be developed and used early in a pandemic, monoclonal antibodies may potentially provide some initial benefit. It is for this reason that we include monoclonal antibodies as an approach that could be considered alongside traditional vaccine R&D. Appendix II provides additional information on monoclonal antibodies. (See text box for examples of COVID-19 monoclonal antibodies).

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<sup>20</sup>The epidermis is the outermost layer of skin, which provides a waterproof barrier and contributes to skin tone. The dermis lies just beneath the epidermis and contains tough connective tissue, hair follicles, and sweat glands.

<sup>21</sup>After the 2009 H1N1 influenza pandemic, several U.S. studies among 2 through 17-year-olds found that the live attenuated influenza vaccine administered intranasally was as effective against influenza B viruses and influenza A (H3N2) viruses as the traditional injectable vaccine, but it was less effective than the injectable vaccines against the 2009 pandemic H1N1 viruses. These data led CDC to recommend against use of this

specific vaccine for the 2016-2017 and 2017-2018 influenza seasons. For more information on the flu mist nasal vaccine, see <https://www.fda.gov/vaccines-blood-biologics/vaccines/fda-information-regarding-flumist-quadrivalent-vaccine>.

<sup>22</sup>Oral poliovirus vaccine is no longer used in the U.S., but it is used in other countries. The U.S. no longer uses the oral poliovirus vaccine due to the risk of vaccine-derived poliovirus disease in certain individuals. However, other oral vaccines have been shown to be safe when not contraindicated.

### COVID-19 monoclonal antibodies

During the COVID-19 pandemic, the Food and Drug Administration (FDA) issued four emergency use authorizations (EUA) for monoclonal antibodies to treat COVID-19. Two of these four treatments consist of a mixture of two monoclonal antibodies, while the remaining two treatments each consist of a single monoclonal antibody. Additionally, researchers are investigating using monoclonal antibodies to protect against COVID-19 before someone is infected or for individuals with compromised immune systems. For example, one developer recently published clinical trial data showing that a mixture of two monoclonal antibodies reduced the risk of people developing any COVID-19 symptoms by 77 percent.

Source: GAO analysis of literature. | GAO-22-104371

## 2.3 Challenges affecting the adoption of R&D technologies and approaches

Drawing on information from experts, stakeholders, and related literature, we identified three key challenges affecting the adoption of technologies and approaches for vaccine R&D:

- Inherent technological limitations
- Complex, costly instruments
- The need for highly trained personnel

### 2.3.1 Inherent technological limitations

The extent to which the following technologies and approaches are adopted may depend on their technological limits.

- **Omics and reverse vaccinology.** Reverse vaccinology cannot predict some antigens—such as sugar-based (polysaccharides) or fat-based (lipids and glycolipids) antigens found in bacteria and parasites—so more traditional approaches are used. Also, individual immune system responses among people vary widely, which may limit the ability to identify common immune responses to antigens even with the use of omics.
- **Next-generation vaccine platforms.** To ensure the effectiveness of next-generation vaccine platforms, vaccine researchers need to carefully consider the selected genetic sequences from pathogens that code for antigens. If they do not, the result can be ineffective vaccine candidates. For example, while the first two mRNA COVID-19 vaccines authorized for emergency use were highly effective at preventing disease, a different mRNA vaccine candidate was not as efficacious in clinical trials.<sup>23</sup> Vaccine researchers stated that this was

<sup>23</sup>In this report, we use the term efficacy to refer to the results of adequate and controlled clinical trial studies that evaluate clinical disease endpoints, and effectiveness to refer to the results of studies carried out under field conditions. For regulatory purposes, FDA determines whether a vaccine is safe and effective, and effectiveness is generally based on the results of adequate and well controlled studies evaluating a clinical disease endpoint (efficacy studies) or a well-accepted immune endpoint (effectiveness studies). For more information on the mRNA vaccine candidate that was not as efficacious in clinical trials, see CureVac, *CureVac Provides Update on Phase 2b/3 Trial of First-Generation COVID-19 Vaccine Candidate, CVnCoV* (Tübingen, Germany / Boston, USA, June 16, 2021).

partly due to the fact that this vaccine candidate lacked key structural modifications to the mRNA that were made in the first two mRNA vaccines.

The cold storage requirements for some vaccines being developed using next-generation vaccine platforms are also a challenge because they require specialized shipping containers and laboratory refrigerators and freezers not readily available at all health care facilities. Vaccines become less effective or completely ineffective if stored at the incorrect temperature. While most vaccines require refrigerated storage at between 2 and 8°C, some mRNA vaccines require storage in freezers at ultra-low temperatures as cold as -80°C.<sup>24</sup>

Challenges associated with cold storage requirements and scaling up the production of vaccines developed using next-generation platforms may affect the ability to use vaccines worldwide. One expert we spoke with noted that these challenges largely impact low and middle income countries.

- **Routes of vaccination.** Nontraditional routes of vaccination require researchers to ensure that the antigen remains capable of producing the required immune response. Some antigens may not be amenable to administration by nontraditional routes. For example, oral vaccines must be developed in such a way that the formulation can survive the harsh gastrointestinal environment. Vaccines

that are administered via nontraditional routes may also require investment in manufacturing capability to accommodate new delivery mechanisms. For example, while various vaccines may be able to be delivered via dermal patches, concerns about costs and mass production have been raised.

- **Monoclonal antibodies.** Monoclonal antibodies differ from vaccines in several ways. For example, they are made of proteins that can degrade over time, do not stimulate the human immune system the same way that vaccines do, and do not provide the long-term protection that vaccines may provide. Also, monoclonal antibodies have traditionally been administered intravenously at a medical facility. However, modifications to specific parts of these proteins can extend the period of protection and may allow for delivery by intramuscular or subcutaneous injection rather than intravenously. Monoclonal antibodies have traditionally been developed for use as therapeutics against non-infectious diseases such as various cancers and autoimmune diseases. Careful assessment, development, and evaluation of safety and effectiveness are important for monoclonal antibodies as for vaccines. More than 100 monoclonal antibodies have been licensed for use by FDA, but

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<sup>24</sup>Some vaccines that require freezer storage, such as the two COVID-19 mRNA vaccines authorized for emergency use in the U.S., can be safely stored for a limited time between 2°C and 8°C. See <https://www.fda.gov/news-events/press-announcements/fda-brief-fda-authorizes-longer-time-refrigerator-storage-thawed-pfizer-biontech-covid-19-vaccine>.

only seven are indicated to treat or prevent infectious diseases.<sup>25</sup>

### 2.3.2 Complex, costly instruments

The extent to which the following technologies and approaches are adopted may also depend on their complexity and cost.

- **Omics and reverse vaccinology.** The high cost of omics-based instruments, such as massively parallel sequencing instruments and their reagents, and the complexity of the resulting data may prevent use by some researchers.
- **Routes of vaccination.** Developing vaccines for different routes of vaccination may be expensive due to complex technologies used in formulation development, according to one expert we spoke to.
- **Monoclonal antibodies.** Traditionally, development and manufacturing of monoclonal antibodies has been complex, expensive, and time consuming. However, new techniques for easier identification, selection, and optimization of monoclonal antibodies have reduced the complexity and time for development from years to weeks. Further, improvements in

manufacturing may decrease production costs.

These potentially high costs and complexity may be exacerbated by the lack of defined or profitable markets, such as vaccines for pathogens with pandemic potential or that primarily affect developing countries. These economic challenges may inhibit new vaccine development.<sup>26</sup>

### 2.3.3 The need for highly trained personnel

The extent to which the following technologies and approaches are adopted may also depend on a highly-trained workforce to operate the complex instruments and processes.

- **Omics and reverse vaccinology.** Because the instruments and techniques, such as massively parallel sequencing instruments and bioinformatics tools, needed for omics analyses are complex, highly-trained personnel may also be needed.
- **Monoclonal antibodies.** The complexity of the technology and approaches for monoclonal antibody development and manufacturing require a specialized workforce. For example, a manufacturing run may require up to two weeks with as many as 10 distinct steps.

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<sup>25</sup>The seven licensed monoclonal antibodies indicated to treat or prevent infectious disease include those for Ebola virus, HIV, *Clostridium difficile*, *Bacillus anthracis* (the organism that causes anthrax), and respiratory syncytial virus. FDA has also issued four EUAs for monoclonal antibodies to treat COVID-19. Two of these four treatments consist of a mixture of two monoclonal antibodies, while the remaining two treatments each consist of a single monoclonal antibody. Most licensed monoclonal antibodies are used as therapeutics for cancer and other non-infectious diseases, such as rheumatoid arthritis.

<sup>26</sup>For additional discussion of economics issues that inhibit vaccine development see Chapter 5.

- **Next-Generation Vaccine Platforms.** The complexity of platform technologies requires a highly skilled workforce, according to an expert we spoke to. For example, for platform technologies, execution of the biological processes is important for consistency of manufactured doses.

## 2.4 Infectious disease prioritization

The federal government supports R&D for infectious disease vaccine development, which is guided, in part, by the Department of Health and Human Services' *Vaccines National Strategic Plan 2021–2025*, among other strategies.<sup>27</sup> This plan provides a strategy to promote vaccine R&D and other areas for the U.S. vaccine and immunization enterprise. Further, the Public Health Emergency Medical Countermeasures Enterprise, which makes recommendations to the Secretary of Health and Human Services, has a list of high-priority biological threats.<sup>28</sup> While this list includes emerging infectious diseases, it does not identify which diseases or disease families have pandemic potential—with the exception of pandemic influenza—for researchers to target development of vaccines against.<sup>29</sup> The Department of Health

and Human Services (HHS) also noted that NIAID publishes a list of priority pathogens.<sup>30</sup> However, this list also does not explicitly prioritize specific potential pandemic pathogens that researchers should consider developing vaccines against, and—as noted on the website—it appears the content has not been reviewed since July 2018. As a result, we have not found evidence that a list which prioritizes specific potential pandemic pathogens for vaccine development exists.

While infectious disease prioritization cannot address potential pandemic pathogens yet to be identified, a strategy for vaccine development against families of known pathogens with pandemic potential could

<sup>27</sup>NIAID has supported and conducted research for vaccines against viral, bacterial, fungal, and parasitic diseases. *The National Health Security Strategy 2019-2022* “provides a vision for strengthening our nation’s ability to prevent, detect, assess, prepare for, mitigate, respond to, and recover from 21st century health security threats.” *The National Influenza Vaccine Modernization Strategy 2020-2030* outlines a vision for the U.S. influenza vaccine enterprise to reduce the impact of seasonal and pandemic influenza viruses.

<sup>28</sup>The *2017-2018 Public Health Emergency Medical Countermeasures Enterprise Strategy* lists high-priority threats. The Public Health Emergency Medical Countermeasures Enterprise also developed a risk assessment framework to assess whether specific emerging pathogens should be included on the list of high-priority threats. These pathogens

may be included if Public Health Emergency Medical Countermeasures Enterprise leadership determines they have the potential to affect national health security.

<sup>29</sup>Some of the functions of the Public Health Emergency Medical Countermeasures Enterprise have been paused since 2018-2020, and only minimal operations have occurred. We previously reported on recent efforts to restructure the Public Health Emergency Medical Countermeasures Enterprise. See GAO, *COVID-19: Continued Attention Needed to Enhance Federal Preparedness, Response, Service Delivery, and Program Integrity*, GAO-21-551 (Washington, D.C.: July 19, 2021).

<sup>30</sup>This list is available at <https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens>.

help with preparedness.<sup>31</sup> As discussed earlier, the speed of COVID-19 vaccine development was unprecedented. Had it not been for two previous coronavirus outbreaks— Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)—and NIH investments in coronavirus research, along with investments in new vaccine platform technologies, the development of a COVID-19 vaccine would have taken significantly longer.

#### **Prioritization of infectious disease**

Experts told us that one way of prioritizing infectious disease could be to use a “stock index fund” approach whereby policymakers select a group of about 100 infectious diseases and work toward making incremental progress on each infectious disease. The experts stated that the rapid development of a vaccine for COVID-19 was largely the result of incremental progress that had been made on developing vaccines for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Using an index fund approach could provide a similar foundation for the development of new vaccines to respond to future epidemics and pandemics. One basis for selecting diseases to include in the “fund” could be by pathogen family so as to leverage progress on one pathogen to others. For example, families of viruses include paramyxoviridae, which include the Nipah virus; orthomyxoviridae, which include influenza viruses; and coronaviridae, which include SARS-CoV-2 that causes COVID-19.

Source: GAO analysis of information from scientific literature and an expert meeting. | GAO-22-104371

Other countries and international entities, such as the United Kingdom, the WHO, and the Coalition for Epidemic Preparedness Innovations, have lists that prioritize pandemic potential pathogens.<sup>32</sup> These lists assist vaccine researchers and developers in prioritizing their vaccine R&D efforts. (See text box for one approach to prioritization.)

NIH officials noted that potential pandemic pathogen prioritization for vaccine development may stifle innovation. HHS officials also noted that such prioritization would not fully address pathogens that are yet to be identified or pathogens that emerge unexpectedly.<sup>33</sup> However, any prioritized list of pandemic potential infectious diseases or disease families used to guide or direct vaccine R&D efforts could be updated

<sup>31</sup>According to researchers from the Johns Hopkins University Center for Health Security, of the 24 families of viruses capable of infecting humans, six families have characteristics that will likely result in one of them being the source of the next pandemic. Those characteristics include no existing immunity in the world’s population, respiratory transmission, transmissible by infected people who have no symptoms, and the lack of any existing, effective therapeutics or vaccines. Such pathogens constitute a global catastrophic biological risk, according to Johns Hopkins University Center for Health Security researchers. The researchers also noted that RNA viruses merit special concern because of their higher tendency to mutate, and they recommended that vaccines against viruses with these characteristics be pursued due to their higher probability to produce global catastrophic biological risk events.

<sup>32</sup>The Coalition for Epidemic Preparedness Innovations is a global partnership launched in 2017 to develop vaccines to stop future epidemics. Its mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines during outbreaks. According to the HHS, NIAID’s public list of priority pathogens includes some of the same pathogens that have been prioritized by the WHO and the Coalition for Epidemic Preparedness Innovations.

<sup>33</sup>As previously noted, the Coalition for Epidemic Preparedness Innovations and the WHO have prioritized pathogen lists for vaccine development that include pathogens that have yet to be identified—termed disease “X.” Johns Hopkins University’s Center for Health Security states that disease X includes those viral families that are likely to cause future catastrophic outbreaks.

periodically to include newly identified threats.<sup>34</sup>

## **2.5 Policy options that may help address challenges related to vaccine R&D**

We identified two policy options that may help address challenges related to the adoption of vaccine R&D technologies and approaches. We define policymakers in this report as a broad term including, for example, Congress, federal agencies, state and local governments, academic and research institutions, and industry.

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<sup>34</sup>The Department of Homeland Security, in coordination with CDC, the Department of Defense (DOD), and the U.S. Department of Agriculture, has created a tiered list of biological terrorism agents that is regularly updated. As part of this effort, these entities conduct a biological threat risk assessment every two years to address shifting priorities or newly identified threats. This bi-annual risk assessment assists in prioritizing R&D of basic biological threat agent research, biosurveillance methods, and the development of countermeasures. This methodology could be likewise used to regularly update a prioritized list of potential pandemic pathogens.



## Policy options that may help address challenges with developing vaccines for infectious diseases

Policy option	Opportunities	Considerations
<p><b>Prioritize infectious disease pathogens</b></p> <p><i>Policymakers could collaborate across sectors (e.g., government, academia, researchers, industry, and nonprofit organizations) to prioritize infectious disease pathogens with pandemic potential for vaccine R&amp;D.</i></p> <p>For example, policymakers could develop a working group to prioritize pathogens with pandemic potential and work more closely with international organizations to prioritize vaccine development as well as develop monoclonal antibodies as prophylactics and therapeutics. The working group could also periodically revisit the prioritized list and update as appropriate to ensure newly identified threats are addressed. This could help address the challenges we identified related to appropriately prioritizing potential pandemic pathogen vaccine R&amp;D efforts and the technologies and approaches needed to support those efforts, address technological limitations, and focus the use of costly instruments and personnel.</p>	<p>Prioritizing pathogens with pandemic potential could improve strategic vaccine R&amp;D decision-making and help focus resources on developing and adopting key technologies and approaches that most effectively address those pathogens.</p> <p>Appropriately matching the technologies and approaches to the prioritized potential pandemic pathogen, then leveraging technologies and expertise held by various entities—such as government, private sector, and academic laboratories—may help address certain technological limitations and costs.</p> <p>With greater leadership and strategic partnerships, policymakers could take steps to increase preparedness to more quickly address threats to the U.S. population.</p>	<p>As new threats are identified, priorities may change, which may cause uncertainty for vaccine developers.</p> <p>Policymakers may have different priorities based on their respective missions; for example, private sector priorities may differ from government priorities.</p> <p>There may be disagreements as to which key technologies should be prioritized and used, resulting in the need for policymakers to weigh the potential advantages and disadvantages associated with various options.</p>
<p><b>Improve preparedness</b></p> <p><i>Policymakers could provide funding and other support for public/private partnerships to strategically address potential pandemic pathogens identified as priorities.</i></p> <p>These partnerships could, for example, develop and test vaccine candidates and monoclonal antibodies that may provide protection from high impact pathogens and pathogens with pandemic potential. Leveraging relationships with the private sector may allow for sharing of highly trained personnel and costs of the complex instruments that are critical parts of the pandemic preparedness infrastructure.</p>	<p>This early development of vaccine candidates and monoclonal antibodies could provide a coordinated foundation that can be mobilized in an emergency. Such an approach could speed vaccine development as well as potentially reduce risk for vaccine researchers and developers concerning questions of safety, efficacy, and manufacturability. Assessing the likelihood of outbreaks from known pathogens, and developing vaccines through at least phase 1 clinical trials may make it easier to more rapidly mitigate future pandemics.</p>	<p>The lack of certainty of the commercial market and government procurement for vaccines against pathogens with pandemic potential may be too risky for the private sector to undertake.</p>

Source: GAO. | [GAO-22-104371](#)

### 3 Technologies and Approaches for Vaccine Testing

Innovative technologies and approaches may enhance vaccine testing, which includes preclinical studies, clinical trials, and post-marketing surveillance studies, allowing vaccine developers to more quickly or effectively test for vaccine safety, identify and recruit clinical trial participants, and analyze clinical trial data. However, challenges, including technological maturity, patient privacy, developing data standards, and the need for stakeholder collaboration, may affect widespread adoption.

#### 3.1 Factors affecting vaccine testing

Numerous factors affect developers' ability to test vaccines, including obtaining animals needed for preclinical studies, recruiting a sufficient number of participants for clinical trials, and managing costs for this portion of development. The mean cost of developing a vaccine from preclinical studies through early clinical safety and efficacy testing (phase 2a) is \$31 million to \$68 million.<sup>35</sup> Further, according to research, about 67 percent of vaccine clinical trials are estimated to fail.<sup>36</sup> Clinical trials may fail for several reasons including failure to

demonstrate that a product produces the desired result (57 percent of failures are for this reason); failure to demonstrate that the product is safe (17 percent); failure to address business challenges, such as keeping costs within budget (22 percent); and failure due to unknown reasons (5 percent).<sup>37</sup>

Developers may also struggle to enroll enough participants. According to a 2015 study, 19 percent of all initiated phase 2 and 3 intervention clinical trials in the National Library of Medicine clinical trial registry either failed to enroll enough participants or completed with less than 85 percent of their expected enrollment, thus reducing the sample size from that planned at trial initiation.<sup>38</sup> For randomized control trials (i.e., those that include both a treatment group and a control group, the typical approach for vaccines), one study from the United Kingdom found that 56 percent of trials between 2004 and 2016 achieved the target number of participants.<sup>39</sup>

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<sup>35</sup>D. Gouglas et al., "Estimating the Cost of Vaccine Development Against Epidemic Infectious Diseases: A Cost Minimisation Study." *The Lancet Global Health*, vol. 6, no. 12 (2018): pp. e1386-e1396.

<sup>36</sup>C. Wong et al., "Estimation of Clinical Trial Success Rates and Related Parameters." *Biostatistics*, vol. 20, no. 2 (2019): pp. 273-286.

<sup>37</sup>These statistics are drawn from a study of trials for new drugs, therapeutic biologics, and vaccines. T. Hwang et al., "Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results," *JAMA Intern Med*, vol. 176, no. 12 (2016): pp. 1826-1833.

<sup>38</sup>B. Carlisle et al., "Unsuccessful Trial Accrual and Human Subjects Protections: An Empirical Analysis of Recently Closed Trials." *Clin Trials*, vol. 12, no. 1 (2015): pp. 77-83.

<sup>39</sup>S. J. Walters et al., "Recruitment and Retention of Participants in Randomised Controlled Trials: A Review of Trials Funded and Published by the United Kingdom Health Technology Assessment Programme," *BMJ Open*, vol. 7, no. 3 (2017).

### 3.2 Technologies and approaches that may enhance vaccine testing

Drawing on information from experts, stakeholders, and the scientific literature, we identified six technologies and approaches that may improve vaccine testing and provide additional methods for assessing data gathered during clinical trials (see table 2). See appendix III for additional information on technologies and approaches related to vaccine testing.

The technologies and approaches we identified can be applied at different phases

of vaccine testing. For example, in the preclinical phase organ chips may be used to determine whether vaccine ingredients have any toxic effects on human cells, which may complement the information gleaned from testing in animals or reduce the need for such testing. Artificial intelligence (AI) and machine learning (ML) may be used for a number of purposes. For example, AI and ML could be used during each phase to predict toxicity in preclinical studies, identify suitable participants for clinical trials, and track long-term side effects during post-marketing surveillance studies (see fig. 4), among other things.<sup>40</sup>

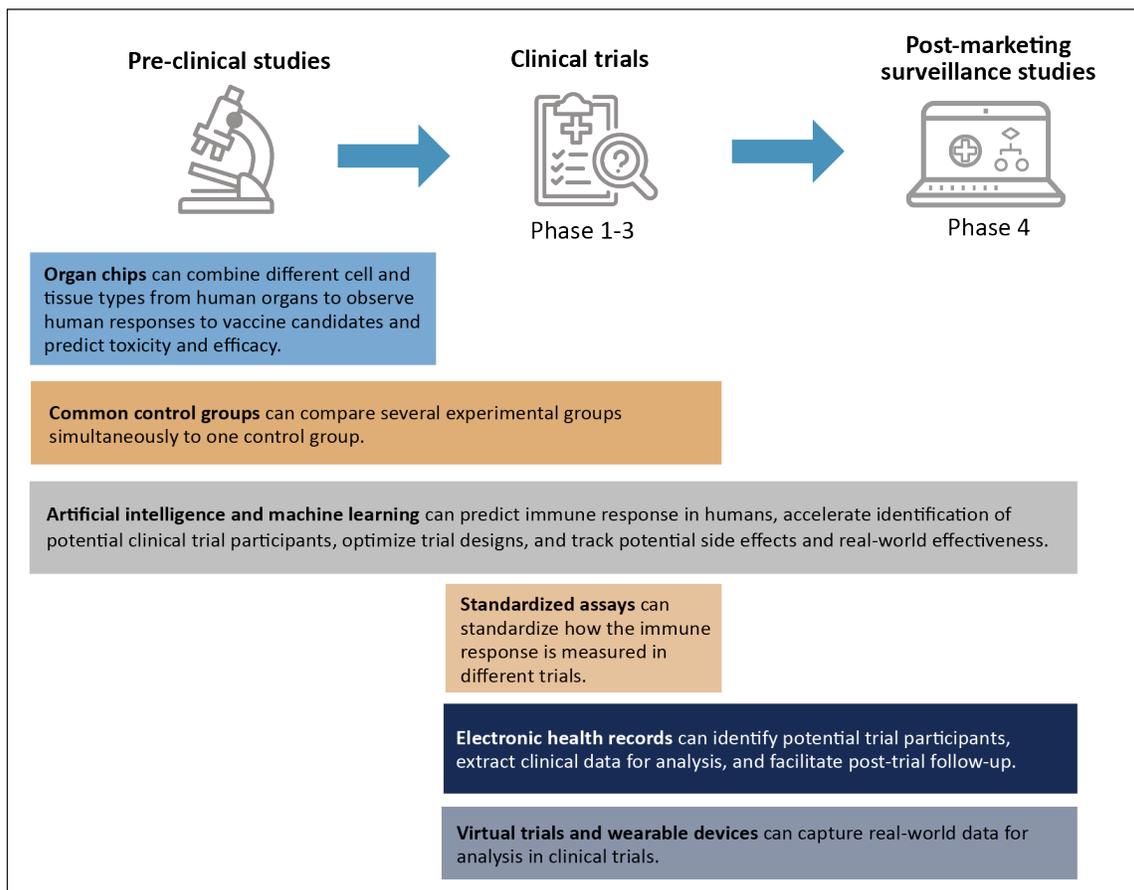
**Table 2: Selected technologies and approaches for vaccine testing**

Name	Description
<b>Organ chips</b>	Populated with cells and used in preclinical studies, organ chips mimic the function of human organs and can be used to study the effect of a vaccine candidate.
<b>Artificial intelligence (AI) and machine learning (ML)</b>	AI and ML systems can analyze large amounts of data gathered during preclinical studies and clinical trials.
<b>Electronic health records (EHR)</b>	An EHR is a digital record of a patient's medical information that can be used to support trials for patient recruitment, clinical data analysis, and post-trial follow-up.
<b>Common control groups</b>	A common control group allows multiple groups of participants in preclinical studies or clinical trials to be compared with a single control group, reducing the number of participants needed or enabling comparison among vaccine candidates.
<b>Standardized assays</b>	Standardized assays are standardized tests or investigative procedures that can potentially be used by different vaccine developers to determine the immune response induced by a vaccine candidate. For example, standardized assays could measure the presence of antibodies in clinical trial participants who have received different vaccines candidates.
<b>Virtual clinical trials and wearable devices</b>	Virtual clinical trials, also referred to as decentralized trials, extend the reach of clinical investigations to where patients live and work. Data for virtual trials can be collected remotely via wearable digital health technologies including watches, bracelets, patches, textiles, and clothing.

Source: GAO. | GAO-22-104371

<sup>40</sup> Post-marketing surveillance studies, also referred to as phase 4 clinical trials, may be required after licensure to obtain additional information on the product's benefits, risks, and optimal use.

**Figure 4:** Selected applications of vaccine testing technologies and approaches



Source: GAO analysis and Sir.Vector/blankstock/stock.adobe.com. | GAO-22-104371

The technologies and approaches we identified may help address factors that affect clinical trials by enabling developers to better collect and analyze safety and efficacy data for various vaccine candidates and more successfully recruit and retain clinical trial participants, among other things (see fig. 5).

**Figure 5: Technologies and approaches that may improve vaccine clinical trials**

 <p><b>Technology /approach</b></p>	<p><b>Safety monitoring</b></p>  <p>Although safety is monitored in each phase of a clinical trial, issues may only become apparent once larger populations participate in phase 3 trials.</p>	<p><b>Recruiting and retaining participants</b></p>  <p>A trial that does not enroll enough participants can result in a sample that is too small to yield valid results.</p>	<p><b>Costs</b></p>  <p>Clinical trials require extensive funding, time, and resources that increase at each successive phase as increasingly larger numbers of volunteers participate.</p>	<p><b>Demonstrating efficacy</b></p>  <p>The primary reason for clinical trial failure is an inability to demonstrate efficacy.</p>
<p><b>Organ chips</b></p>	<p>May complement animal testing to predict a vaccine candidate's toxicity in humans prior to clinical trial testing in humans.</p>	<p>N/A</p>	<p>May reduce the number of animals needed for preclinical studies.</p>	<p>N/A</p>
<p><b>Artificial intelligence and machine learning</b></p>	<p>May predict whether a vaccine candidate may cause a low or high number of adverse side effects and may identify rare adverse events from safety reports.</p>	<p>May identify potential participants by assessing suitability from health records and other patient data.</p>	<p>May save money by identifying design efficiencies, such as the ideal number of participants to enroll and the optimal dosage.</p>	<p>May analyze clinical and immunological data from trials and predict antibody response in humans, thereby identifying the immune protection a vaccine candidate may provide.</p>
<p><b>Common control groups</b></p>	<p>May allow for evaluating safety data across multiple vaccine candidates.</p>	<p>May increase a patient's chance of receiving a vaccine candidate, which could help with recruiting patients to clinical trials.</p>	<p>May save money since fewer participants are needed when comparing experimental groups to a single control group.</p>	<p>May allow for evaluating efficacy data across multiple vaccine candidates.</p>
<p><b>Standardized assays</b></p>	<p>N/A</p>	<p>N/A</p>	<p>N/A</p>	<p>May establish a standard measurement approach that allows for head-to-head vaccine candidate comparisons.</p>
<p><b>Electronic health records</b></p>	<p>May be used in safety surveillance to answer specific safety questions about vaccine candidates.</p>	<p>May help identify which individuals receiving care in a health system meet study criteria as eligible participants.</p>	<p>May save money and time by centralizing data collection with an electronic clinical trial management system.</p>	<p>May provide data that can be analyzed for clinical trials.</p>
<p><b>Virtual trials and wearable devices</b></p>	<p>May allow for continuous safety monitoring of vaccine candidate side effects.</p>	<p>May expand the pool of potential participants and enable remote data capture, which reduces barriers to participation.</p>	<p>May save money after the initial expense of adopting the technology.</p>	<p>May collect data continuously, potentially providing a more complete picture of participants' health during the trial.</p>

Source: GAO analysis and SergeyCherednichenko/dzm1try/kornkun/blankstock/stock.adobe.com. | GAO-22-104371

### 3.3 Challenges affecting the adoption of vaccine testing technologies and approaches

Based on information from experts, stakeholders, and the scientific literature, we identified four challenges affecting the adoption of technologies and approaches for vaccine testing:

- Limited technological maturity
- Difficulty protecting patient data
- Ongoing data standards development
- Limited stakeholder collaboration and agreement on common approaches to testing

These challenges may affect vaccine developers, researchers who conduct clinical trials, and patients who participate.

#### 3.3.1 Limited technological maturity

The extent to which the following technologies and approaches are adopted will depend on their technological maturity or ability to demonstrate validity.

- **Organ chips.** Organ chips are not yet mature enough to replicate many of the complex functions and responses of the human immune system, limiting their applicability. Specifically, according to

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<sup>41</sup>The innate immune system is the body's first line of defense against germs entering the body. It consists of protection offered by the skin, mucous membranes, immune system cells, and proteins. The adaptive immune system responds if the innate immune system is not able to destroy the germs. It is made up of T-lymphocytes, B-lymphocytes, and antibodies.

<sup>42</sup>The Health Insurance Portability and Accountability Act Privacy Rule establishes the conditions under which protected

NIH, organ chips replicate the innate immune response, but the ability to replicate the adaptive immune response is still being developed.<sup>41</sup> While organ chips can be used for some aspects of toxicity testing, further maturity may be needed to demonstrate that they do not produce false negative results.

- **Virtual trials and wearable devices.** To conduct fully virtual trials, many organizations will need to develop new technical capabilities. For example, they will need to integrate wearable technologies and develop ways to capture and analyze potentially large volumes of data. Many wearable devices are in early development and will need to demonstrate analytical and clinical validation to support data submitted for vaccine licensure.

#### 3.3.2 Challenges protecting patient data

When patients consent to allow data from their health records and other sources to be made available for use in trials, more people gain access to this information, and the challenge of protecting data privacy increases.<sup>42</sup> Researchers conducting clinical trials must adhere to federal privacy laws and regulations, such as the Health Insurance Portability and Accountability Act Privacy Rule and other relevant requirements.<sup>43</sup>

health information may be used or disclosed for research purposes. Researchers may obtain an individual authorization from the patient that meets the requirements set out in the Privacy Rule or they may seek an institutional review board or privacy board waiver of the Privacy Rule's authorization requirement. 45 C.F.R. §§ 164.508, 164.512(i)(1)(i).

<sup>43</sup>A HIPAA-covered entity may also "de-identify" patient data in accordance with the Privacy Rule prior to sharing it for research purposes. 45 C.F.R. §§ 164.502(d), 164.514. This is

Technologies and approaches directly affected by the need to protect patient data include:

- **Electronic health records (EHR).** EHRs contain a wealth of sensitive information including patients’ social security numbers, addresses, and health diagnoses.
- **AI and ML.** AI and ML systems that are deployed in clinical settings contribute to privacy risks, and there are concerns that the use of increasingly sophisticated computer techniques could make it easier to re-identify data from patient records and other sources.
- **Virtual trials and wearable devices.** Virtual trials collect data outside the traditional clinical care setting. There is a need for security in the transmission of data. Researchers must maintain protections in accordance with the Privacy Rule.

### 3.3.3 Ongoing data standards development

In 2020, the HHS Office of the National Coordinator for Health Information

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typically done by removing data fields such as names, social security numbers, account numbers, and full faced photographs. However, studies have shown that even properly de-identified data may retain some risk of re-identification.

<sup>44</sup>21st Century Cures Act: Interoperability, Information Blocking, and the Office of the National Coordinator for Health Information Technology Health IT Certification Program, 85 Fed. Reg. 25,642 (May 1, 2020). Interoperability and Patient Access Final Rule, and 85 Fed. Reg. 25,510 (May 1, 2020). The Office of the National Coordinator for Health Information Technology’s final rule establishes new rules to prevent “information blocking” practices by healthcare providers, developers of certified health information technology, and other entities as required by the 21st Century Cures Act. Pub. L. No. 114-255, § 4004, 130 Stat. 1034, 1176 (2016). The Centers for Medicare & Medicaid Services’ final rule requires, among

Technology and the Centers for Medicare & Medicaid Services issued final rules that require data exchange and data element standards for use in EHRs in order to promote interoperability—generally defined as the ability of a system to exchange electronic health information with, and use electronic health information from other systems, without special effort on the part of the user.<sup>44</sup> This includes the use of technical standards for transmitting EHR data and vocabulary standards for the content of EHR data.<sup>45</sup>

HHS has identified the need for securely available electronic health information since 2015, and has stated that it expects improved interoperability to benefit researchers. Specifically, due to a lack of data standards and interoperability in the past, researchers have been hindered in their ability to use EHRs for research including clinical trials. The new rules may help address the following challenges to the use of EHRs in clinical trials:

- **Lack of consistency in health record data.** For some kinds of clinical data, standards either have not been previously developed or have not been universally adopted. This inconsistency has hindered

other things, that health plans in Medicare Advantage, Medicaid, the Children’s Health Insurance Program, and the federal exchanges make certain data available to patients through an application programming interface.

<sup>45</sup>Key requirements of the Office of the National Coordinator for Health Information Technology and the Centers for Medicare & Medicaid Services rules are (1) the adoption of the Health Level 7 (HL7®) Fast Healthcare Interoperability Resources application programming interface standard, which enables health information technology systems and applications to receive and exchange information from EHRs and (2) adoption of the United States Core Data for Interoperability standard, which is a common set of data elements, organized by data classes, that use a standardized content and format.

the ability to use criteria to identify eligible patients and analyze data from EHRs.

- **Lack of EHR interoperability.** EHR data have in the past been based on different data standards that cannot be exchanged easily. A lack of widely adopted data standards has hindered the exchange of data between EHRs and electronic data capture systems, which researchers use to collect and manage clinical trial data.<sup>46</sup>

While improved interoperability is expected to benefit researchers who use EHRs, new data standards may affect how researchers are able to use data. The Office of the National Coordinator for Health Information Technology stated that while standardized data elements successfully gather general structured information, these data are limited and often insufficient for clinical trials, which require data that can answer specific research questions. It also stated that researchers may need to supplement these data from sources outside the EHR, such as genomic data, but these data are not currently available using the adopted standard. Additionally, data standards are still being developed, which may affect the availability of data elements for research, including for clinical trials.<sup>47</sup>

Expanding and implementing standards for electronic health data requires cooperation between health care providers, government, and industry. Industry representatives told us there's a need to develop implementation

guidance collaboratively and that even with data standards in place, it will be difficult for researchers to use EHR data in clinical trials without additional guidance. If efforts to develop standards and advance interoperability do not continue to incorporate the specific needs of the research and clinical trial communities, researchers may be unable to optimize the potential for electronic health data to be used in clinical trials.

### 3.3.4 Limited stakeholder collaboration and agreement on common approaches to vaccine testing

Using common approaches, such as standardized assays and common control groups, allows for direct comparisons among multiple vaccine candidates. However, vaccine developers traditionally test their vaccines candidates using their own assays and recruit their own participants for clinical trials because companies tend to operate independently. Also, the tasks involved to develop assays and plan trials are often closely integrated, and the timing of clinical trials for different vaccines would need to align in order to use a common control group. Using developer-specific approaches to vaccine testing makes it more difficult to compare data from clinical trials of more than one vaccine candidate and determine the relative efficacy of each. While experts said it is important for different kinds of vaccines to be developed during a pandemic, they also

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<sup>46</sup>Food and Drug Administration, *Use of Electronic Health Record Data in Clinical Investigations* (Silver Spring, Md.: July 2018).

<sup>47</sup>For example, the Office of the National Coordinator for Health Information Technology's final rule states that clinical notes would be included within the United States Core Data for

Interoperability standard and it adopts eight types of clinical notes as standard data elements. Version 2 of the United States Core Data for Interoperability standard was released in July 2021 and it includes only five data elements within the clinical notes data class: consultation note, discharge summary note, history & physical, procedure note, and progress note.

said it is important to be able to directly compare the results to better understand the potential differences in protection provided by each vaccine candidate. Stakeholders, including vaccine developers and government decision-makers, would need to collaborate to use standardized assays and common control groups in order to benefit from the advantages they may provide.

According to experts we met with, it may be feasible and advantageous to use standardized assays and common control groups in some scenarios. For example, when government invests in developing a vaccine, it has an opportunity to work with industry stakeholders to design clinical trials that include these features. Experts said master protocols, also known as common protocols (a common set of processes that govern a set of studies), could be developed that include the use of standardized assays and common control groups that vaccine developers could agree to follow in vaccine testing.<sup>48</sup> The protocols would ideally be developed prior to the onset of a pandemic event, according to experts, but the approach might also be possible in an emergency.

The master protocol approach has been used previously with therapeutics, including for COVID-19, but HHS officials told us COVID-19 vaccine developers maintained control over their own trial protocols. However, it may be possible to incentivize developers to agree to master protocols by completing formative

work such as the difficult process of developing assays, or by tying government funding for vaccine development to the use of master protocols. One expert told us that expanding inventories of available assays for pathogens and families of pathogens could expedite the development and testing of new vaccine candidates. Another expert told us that developing standardized assays to measure cellular response to vaccine candidates could streamline the evaluation of vaccine efficacy during clinical trials.

According to NIH officials, however, developing meaningful master protocols for using standardized assays and common control groups in advance of a pandemic outbreak from a novel pathogen would be challenging. According to officials, the development of assays can require substantial investment of time and resources to ensure their safety, validity, and reproducibility, and this would likely need to be done for each individual pathogen. Furthermore, officials said adopting common control groups across multiple vaccine developers' vaccine trials also requires care, particularly if there are differences in the doses required or the timing of when different vaccine companies are ready to begin clinical trials. NIH officials said there may be ways to address these challenges, however. They said NIH's Rapid Acceleration of Diagnostics program is an example of early-stage government investment to jump-start diagnostic development when a new infectious agent

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<sup>48</sup>FDA guidance defines a master protocol as a protocol designed with multiple sub-studies, which may have different objectives and involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure. FDA, *COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention* (Silver Spring, Md.: May 2021).

threatens public health, and NIH’s clinical trial evaluating mixed COVID-19 vaccine schedules serves as a model for addressing these challenges.

One expert stated that even if standardized assays are not ready at the start of a clinical trial, once the assays are available they can be used on stored samples from trials. The expert said that this approach could be part of the protocols and could help in making comparisons across vaccine candidates. Furthermore, according to the expert, when the federal government is contributing funding it could also encourage companies to share biological samples and establish common definitions of infection and disease, which would help improve the ability to compare results across vaccine candidates.

As part of the response to the COVID-19 pandemic, NIH’s Accelerating COVID-19 Therapeutic Interventions and Vaccines partnership initiative used some common protocols, including standardized assays, to guide phase 3 clinical trials of certain COVID-19 vaccines (see text box for an example of how harmonized protocols have been used).<sup>49</sup>

#### Harmonized protocols for COVID-19 vaccine candidates

The National Institutes of Health (NIH)-led Accelerating COVID-19 Therapeutic Interventions and Vaccines is a public-private partnership that was formed to speed development of the most promising treatments and vaccines for COVID-19 by coordinating activities by federal agencies, vaccine developers, and other stakeholders. The partnership advised on protocol designs to harmonize the approach to phase 3 clinical trials for COVID-19 vaccines conducted through the National Institute of Allergy and Infectious Diseases’ (NIAID) COVID-19 Prevention Network.<sup>50</sup>

Features of the harmonized protocols included:

- **Standardized assays.** Standardized assays were developed collaboratively and were used to evaluate the efficacy of COVID-19 vaccine candidates in phase 3 clinical trials.
- **Shared data and safety monitoring board.** Clinical trials were overseen by a single shared independent data safety monitoring board, established by NIAID.
- **Separate control groups.** Phase 3 clinical trials for COVID-19 vaccine candidates maintained separate control groups for each vaccine trial.

According to NIH, clinical trials of COVID-19 vaccines conducted through NIAID’s COVID-19 Prevention Network used these standardized assays. The Accelerating COVID-19 Therapeutic Interventions and Vaccines partnership coordinated efforts helped address challenges related to enrolling enough participants for trials and interpreting and comparing trial results.

Source: GAO analysis of information from scientific literature and an expert meeting. | GAO-22-104371

Experts said that the Accelerating COVID-19 Therapeutic Interventions and Vaccines partnership could provide a model for using master protocols for vaccine clinical trials. Following this approach, stakeholders could collaborate to develop protocols and could follow the protocols to advance vaccine candidates to phase 1 clinical trials. Once a

<sup>49</sup>The Accelerating COVID-19 Therapeutic Interventions and Vaccines public-private partnership is coordinated by the Foundation for the National Institutes of Health and brings together NIH, the Biomedical Advanced Research and Development Authority (BARDA), CDC, FDA, DOD, the Department of Veterans Affairs, the HHS-DOD COVID-19 Countermeasures Acceleration Group (formerly known as

Operation Warp Speed), the European Medicines Agency, and representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies.

<sup>50</sup>According to NIH, the harmonized approach was intended to guide vaccine developers. However, developers still designed their own specific clinical trial protocols.

pandemic event occurs, the protocols could be modified as necessary, according to experts. Such protocols could also guide phase 3 clinical trials as was done for COVID-19 vaccine candidates.

Although the Accelerating COVID-19 Therapeutic Interventions and Vaccines partnership did not use common control groups—and they may not be applicable in every scenario—experts told us that doing so has the potential to improve trial recruitment and might enable adaptive designs that could speed up clinical trials involving multiple vaccine candidates.<sup>51</sup> Along with the adoption of data standards, which may improve the readiness of EHRs for use in clinical trials, these potentially allow for more efficient means to enhance the response to endemic levels of infectious disease as well as better respond to potential future epidemics and pandemics.

### 3.4 Policy options that may help address challenges related to vaccine testing

We identified two policy options that may help address challenges related to the adoption of testing technologies and approaches. As mentioned previously, policymakers include Congress, federal agencies, state and local governments, academic and research institutions, and industry.

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<sup>51</sup>FDA defines an adaptive design as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. FDA, *Adaptive Designs for Clinical Trials of Drugs and Biologics* (Silver Spring, Md.: Nov. 2019).



**Policy options that may help address challenges related to vaccine testing**

Policy option	Opportunities	Considerations
<p><b>Further support development of data standards</b>  <i>Polymakers could further support coordinated efforts to obtain the views of all stakeholders and to develop standards for health data and their use in clinical trials.</i>            This support could help address the challenge we identified related to ongoing data standards development.</p>	<ul style="list-style-type: none"> <li>Integrating researchers’ needs into the standards development process could better ensure the necessary data are available.</li> <li>Data standards could more easily allow researchers to combine different data sets, enabling better transmission of data for analysis in trials.</li> <li>Interoperable systems may eliminate the manual transcription of data, reducing data entry errors.</li> <li>Access to high-quality data in a standardized format may allow streamlined patient recruitment for clinical trials.</li> <li>Improving standards may facilitate identification of differences in clinical trial efficacy across population subgroups (e.g., differences by age, race, and gender) by broadening the pool of patient records available for research.</li> </ul>	<ul style="list-style-type: none"> <li>Expanding access to patient health data requires attention to ensure privacy. If patient data have been de-identified, combining data from multiple sources may make it easier to re-identify.</li> <li>Data from different sources, such as wearable devices and clinical notes, may vary in quality and reliability, making it difficult to use them in combination.</li> <li>Developing and implementing standardized data formats and IT infrastructure is time-consuming and costly.</li> <li>Disparities in access to health care, particularly among some population groups, may limit the pool of patient records available for research.</li> </ul>
<p><b>Study feasibility of using common control groups and standardized assays</b>  <i>Polymakers could study the feasibility of collaborating with industry for use of standardized assays and common control groups during pandemic and non-pandemic scenarios.</i>            This option could help address the challenge we identified related to limited stakeholder collaboration and agreement on common approaches to testing.</p>	<ul style="list-style-type: none"> <li>Trial logistics could be streamlined, and cost-sharing could produce savings.</li> <li>Meeting recruitment goals could be faster, which can be important during pandemics.</li> <li>Trial participants are more likely to receive a vaccine candidate, which may boost recruitment.</li> <li>Incorporating adaptive trial designs in planned protocols may lessen regulatory review requirements when modifications need to be made.</li> <li>A head-to-head comparison of vaccine candidates, enabled by following master protocols, improves understanding of efficacy. The master protocol approach may also facilitate the implementation of clinical research across successive outbreaks of a disease since protocols will already be in place.</li> </ul>	<ul style="list-style-type: none"> <li>Vaccine developers may be unwilling to give up control of designing trials and use of proprietary assays, and may resist having head-to-head comparisons with other vaccine candidates.</li> <li>If not agreed to in advance, stakeholder coordination, infrastructure requirements, and complex trial design elements could make the start-up time for a master protocol longer than that of a single-purpose trial.</li> <li>Determining the timing and predicting the required funding level could be difficult if new vaccine candidates will be added to a trial design on an ongoing basis.</li> <li>Developing assays requires significant effort. Harmonizing results across vaccine candidates, as was done for COVID-19 phase 3 clinical trials, may be more achievable than requiring developers to use a standardized method to measure immune response.</li> </ul>

Source: GAO. | GAO-22-104371

## 4 Technologies and approaches for vaccine manufacturing

Certain technologies and approaches for vaccine manufacturing may have the potential to enhance the U.S.'s ability to address infectious diseases and prepare for future epidemics and pandemics. These technologies and approaches may allow for an increase in manufacturing flexibility—the ability to quickly switch from manufacturing one vaccine to another—and an increase in manufacturing productivity. However, challenges such as technical limitations, costs, and the need for highly trained personnel affect vaccine manufacturers' ability to adopt new technologies and approaches. Further, private manufacturers may be reluctant to establish and maintain costly excess manufacturing capacity to address surges in vaccine demand during pandemics. The federal government has attempted to address these issues; however, challenges remain.

### 4.1 Factors affecting vaccine manufacturing

Factors that affect vaccine manufacturing include:<sup>52</sup>

- A lack of flexibility to rapidly switch manufacturing lines from one vaccine to another

- An inability to rapidly scale up manufacturing to meet surges in new vaccine demand
- An inability to use available capacity to manufacture new vaccines without impacting the manufacture of other licensed vaccines

Vaccine manufacturing is traditionally inflexible, with many manufacturers producing single vaccine products in centrally located, dedicated facilities. As a result, new vaccines cannot be easily incorporated into existing facilities, and different vaccines cannot be manufactured simultaneously, in quick succession, or closer to the geographic point of need. Further, centrally located, dedicated product manufacturing facilities can be a single point of failure—a risk that can negatively impact vaccine supply.

Besides influenza vaccine manufacturing, the U.S. lacks the infrastructure—known as surge capacity—needed to quickly scale up the manufacture of new vaccines to address outbreaks, including pandemics. The lack of surge capacity is caused partially by the reluctance of vaccine manufacturers in the private sector to invest in the high cost of maintaining excess, idle capacity in anticipation of unknown future vaccine

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<sup>52</sup>As noted in GAO-21-207, vaccine manufacturing supply chains may be strained by disruptions caused by the COVID-19 pandemic, including changes in the labor market, increases or decreases in the demand for certain goods, or export restrictions implemented by some countries. For example, obtaining manufacturing materials, such as disposable reactor bags, reagents, and certain chemicals, may be a challenge. Further, the supply of materials used in fill-finish manufacturing, such as glass vials and pre-filled syringes, may be limited.

needs. As a result, U.S. manufacturing capacity is generally focused on meeting market demand for vaccines listed on the child and adolescent immunization schedule (e.g., measles, mumps, rubella, and polio) and those on the adult immunization schedule for which profitable markets exist (e.g., shingles and pneumonia).<sup>53</sup>

To increase U.S. surge capacity, the Biomedical Advanced Research and Development Authority (BARDA), within HHS's Office of the Assistant Secretary for Preparedness and Response, established three Centers for Innovation in Advanced Development and Manufacturing in June 2012.<sup>54</sup> Among other capabilities, these centers were designed to provide technical assistance and to support additional surge capacity that would be capable of delivering finished doses of pandemic vaccine within 12 weeks of the declaration of a pandemic.<sup>55</sup> However, as noted by representatives from these centers that we spoke with, these facilities had difficulties in

maintaining operational readiness. Further, in congressional testimony, a representative from another center noted the challenge of maintaining operational readiness.<sup>56</sup> These centers' facilities also needed retrofitting, such as equipment and facility upgrades, to be able to sufficiently and timely manufacture the vaccines needed to respond to the COVID-19 pandemic.

## 4.2 Technologies and approaches for vaccine manufacturing

Drawing on information from experts, stakeholders, and the scientific literature, we identified five selected technologies and approaches that may improve vaccine manufacturing—collectively known as bioprocess intensification (see table 3). These selected technologies and approaches are not necessarily new: some have been used for years in other industries, including chemical and pharmaceutical manufacturing, and some have already been applied in vaccine

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<sup>53</sup>The child and adolescent immunization schedule includes recommended vaccines for children from birth through age 18. The adult immunization schedule includes recommended vaccines for ages 19 years and older.

<sup>54</sup>Created as public-private partnerships, the three Centers for Innovation in Advanced Development and Manufacturing were established to address influenza pandemic vaccine availability, which fell short in 2009 because of an outdated egg-based manufacturing process and bottlenecks in the fill-finish step. The term fill-finish refers to the process of filling sterile containers with vaccine and finishing the process of packaging filled containers for distribution. To address the fill-finish bottlenecks, the federal government established the Fill Finish Manufacturing Network, a group of pre-qualified facilities that fill and finish vaccines for manufacturers in a public health emergency. See GAO, "National Preparedness: HHS Has Funded Flexible Manufacturing Activities for Medical Countermeasures, but It Is Too Soon to Assess Their Effect," [GAO-14-329](#) (Washington, D.C.: March 31, 2014).

<sup>55</sup>While the 12-week goal is specific to an influenza pandemic, the capacity and capabilities developed for pandemic influenza preparedness could enable HHS to respond more effectively to other emerging infectious diseases. HHS's Office of the Assistant Secretary for Preparedness and Response's goal is to provide 600 million doses of pandemic vaccine for the U.S. within 6 months or less after a pandemic is declared.

<sup>56</sup>Transcript from "Examining Emergent Biosolutions' Failure to Protect Public Health and Public Funds Hearing Before the Select Subcommittee On The Coronavirus Crisis of the Committee on Oversight and Reform House of Representatives One Hundred Seventeenth Congress First Session May 19, 2021".

manufacturing processes. These technologies and approaches may help vaccine manufacturers increase flexibility and capacity by allowing for rapid switching between different vaccines within the same facility, increasing productivity to help

manage surge demand, and potentially distributing manufacturing closer to points of need. See appendix IV for additional information on technologies and approaches related to vaccine manufacturing.

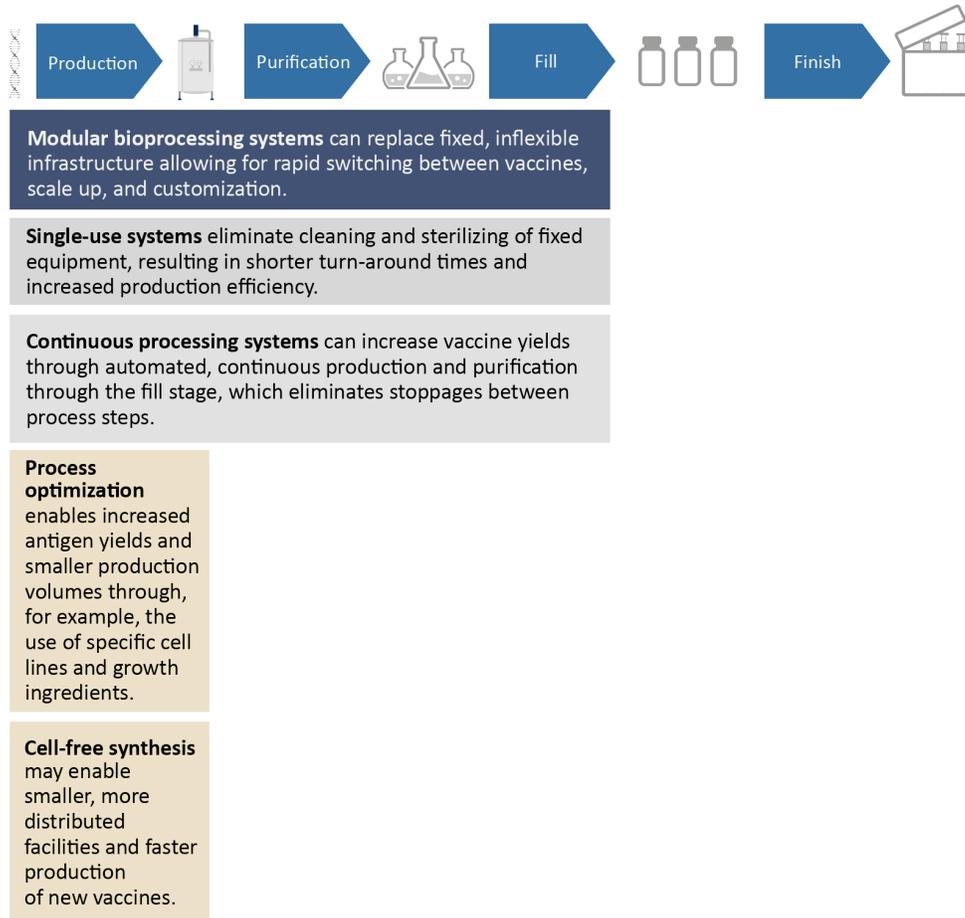
**Table 3: Selected technologies and approaches for vaccine manufacturing**

Name	Description
<b>Single-use systems</b>	Single-use systems refer to bioprocessing equipment that is designed to be used once and then discarded. Such equipment is generally composed of sealed, pre-sterilized, plastic components.
<b>Modular bioprocessing systems</b>	These systems divide the manufacturing process into smaller functional building blocks known as modules, suites, or pods that can stand alone or be incorporated into an existing facility. For example, new modules can be added to quickly expand capacity or switched to rapidly change processes, according to an expert we spoke to.
<b>Cell-free synthesis</b>	Biological enzymes—proteins that cause biochemical reactions—are used to generate antigens, which are then combined with other materials to create vaccines.
<b>Process optimization</b>	This approach improves the cells and growth ingredients—known as medium—and other processing steps. According to an expert we interviewed, this technology may increase productivity and allow manufactures to get more out of the same equipment or facility.
<b>Continuous manufacturing systems</b>	These systems use automated, high-throughput, small-footprint production and purification equipment to manufacture vaccines. In contrast to existing batch processing methods, which use separate tanks for each step in the process, continuous manufacturing allows all steps of vaccine production to continue without interruption as the materials flow through the system.

Source: GAO. | [GAO-22-104371](#)

The technologies and approaches we identified can be applied at different stages of vaccine manufacturing. For example, modular bioprocessing systems may replace fixed, inflexible infrastructure, potentially allowing for rapid switching between vaccines, scale up, and customization. Process optimization can enable vaccine manufacturers to increase antigen yields and use smaller production volumes through, for example, the use of specific cell lines and growth ingredients (see fig. 6).

**Figure 6: Selected applications of vaccine manufacturing technologies and approaches**



Source: GAO analysis of scientific literature and rashadashurov/tutti\_frutti/StockBURIN/divstock/stock.adobe.com. | GAO-22-104371

Single-use systems may help vaccine manufacturers increase the flexibility of their vaccine manufacturing facilities. For example, manufacturers can replace traditional stainless-steel vessels—known as bioreactors—that are used to grow the cells that produce antigens with disposable plastic bioreactor bags. Single-use systems eliminate the need for cleaning and sterilizing fixed equipment between vaccine manufacturing runs—also known as batches—resulting in shorter turn-around times and increased efficiency. Since they are discarded after each use, single-use systems may also reduce the potential for contamination caused by inadequate cleaning or sterilization.

Modular bioprocessing systems may also help vaccine manufacturers increase the flexibility of their facilities. For example, a vaccine facility’s fixed infrastructure, such as rooms and areas dedicated to specific bioprocessing steps, can be replaced with modular components. These modular components can allow manufacturers to rapidly switch from manufacturing one vaccine to another, scale up manufacturing, or add a new facility in a new location more quickly, according to an expert we spoke to. Modular bioprocessing systems also allow vaccine manufacturers to continuously customize and reconfigure their equipment to accommodate new vaccines or processes more quickly—changes that are

traditionally difficult and costly. This ability to customize bioprocesses could allow vaccine manufacturers to establish smaller vaccine manufacturing facilities at sites closer to infectious disease outbreaks.

For some vaccines, cell-free synthesis may eliminate the need to grow living cells to produce the antigen of interest, potentially resulting in smaller, more distributed facilities, and faster manufacture of new vaccines in existing facilities. Cell-free synthesis combines purified biological molecules to produce antigens, which are then purified and formulated into vaccines.<sup>57</sup> Additionally, while the first step in mRNA vaccine manufacturing involves traditional growth of cells to generate a key component—DNA—needed to make the vaccine, the subsequent step to manufacture the mRNA uses cell-free synthesis. The flexibility of cell-free synthesis reduces the single point of failure risk that may be associated with centrally located, dedicated product facilities. Further, cell-free synthesis may allow for the simultaneous manufacture of different vaccine antigens within the same facility, which cannot be done in most existing facilities.

Process optimization allows manufacturers to increase antigen yields through, for example, the use of cells specifically developed to increase antigen productivity, known as optimized cell lines, matched with specific growth ingredients, known as

growth medium. Antigen productivity can be increased by growing cells at higher densities.<sup>58</sup> High-cell density can be achieved by selecting for or artificially modifying cells that grow to high densities or by changing how the cells are grown. For example, cells that freely grow in liquid medium—called suspension cultures, typically result in higher cell densities and antigen yields than cells that have been adapted to grow attached to a surface, called adherent cultures.

Continuous manufacturing systems may also increase vaccine yields through automated, continuous antigen production and purification. Continuous manufacturing systems may run for weeks or even months, reducing, for example, the requirement to start new cell cultures for antigen production, stoppages between production and purification steps, and the potential for contamination. For example, one manufacturer we spoke with has tested its closed-production systems with continuous downstream processing technology to produce vaccines for clinical trials.<sup>59</sup>

### 4.3 Challenges affecting the adoption of vaccine manufacturing technologies

Drawing on information from experts, stakeholders, and the scientific literature, we identified three key challenges that

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<sup>57</sup>Cell-free synthesis uses a number of purified biological molecules, including enzymes and nucleic acids.

<sup>58</sup>Cell density describes the number of cells in a specific volume of growth medium.

<sup>59</sup>A closed-production system uses equipment designed and operated in such a way that the product is not exposed to the room environment. Materials may be introduced to a closed system, but exposure of the product to the room environment must be avoided.

affect the adoption of technologies for vaccine manufacturing:

- Inherent technological limitations
- High costs and the need for highly trained personnel
- Business risk

#### 4.3.1 Inherent technological limitations

The extent to which some technologies and approaches are adopted for vaccine manufacturing will depend on their technological limits.

- **Single-use systems.** Some of the plastic materials used in single-use systems may leach unwanted substances into the process, and disposable bioreactor bags may leak.<sup>60</sup> Also, limitations in disposable bioreactor scale require scale out versus scale up, according to an expert we spoke to. Further, there are concerns about the environmental impact of the waste plastic materials used in single-use systems after disposal.
- **Cell-free synthesis.** Cell-free systems may be unable to synthesize some proteins, such as sugar-based (polysaccharide) antigens, or to produce properly folded or modified proteins.

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<sup>60</sup>Because these leachable substances may be present, manufacturers perform extensive testing to ensure that single-use systems do not negatively impact the vaccine and so that batches do not need to be discarded, according to an expert we spoke to.

- **Continuous manufacturing.** Continuous manufacturing cannot be used for all types of vaccines. For example, vaccines produced in eggs, such as most seasonal influenza vaccines, cannot use continuous manufacturing processes. Additionally, continuous manufacturing processes cannot be used for some vaccines because the biochemical processes by which cells produce the antigens are not well defined and the ability to control the production process is limited.

Changing from batch to continuous manufacturing also presents challenges because depending on the circumstances, vaccine companies also may be required to seek and obtain FDA approval of manufacturing changes prior to vaccine distribution to ensure the safety and effectiveness of the vaccine have not been adversely affected.<sup>61</sup>

#### 4.3.2 High costs and the need for highly trained personnel

The extent to which some technologies and approaches are adopted will also depend on their cost and need for specialized personnel. For example, these technologies require upfront capital expenditures by manufacturers that may be prohibitively expensive. Further, manufacturers may be reluctant to replace equipment for which

<sup>61</sup>A sponsor may be required to seek and obtain FDA approval of certain changes to an existing biologics license application to ensure the safety and effectiveness of the biologic has not been adversely affected. This may include changes to the product, production process, quality controls, equipment, facilities, or responsible personnel. See 21 C.F.R. § 601.12 (2020).

they have already made significant capital expenditures.

- **Single-use and modular bioprocessing systems.** Modular bioprocessing systems may involve significant capital expenditures to implement. However, once implemented, single-use and modular bioprocessing systems may reduce operational costs and increase efficiencies that offset upfront expenses. Further, building an integrated modular facility requires more skill and expertise, including technical construction and qualified, experienced personnel to get a facility fully operational.
- **Continuous bioprocessing.** The costs involved in developing new infrastructure and adding new equipment and automation for continuous processing may discourage the use of this technology. Further, the skill set and capabilities required to design, develop, validate, and operate a continuous flow process are different from those required for conventional batch processing.<sup>62</sup>

#### 4.3.3 Business risk

The extent to which some technologies and approaches are adopted may also depend on how manufacturers perceive the business risk. Manufacturers may face uncertainty in how regulators will evaluate

a new vaccine manufacturing technology and how that could affect its financial viability. According to a National Academies of Sciences, Engineering, and Medicine report that was sponsored by FDA, if introducing an innovative technology might result in additional activities, costs, and time to support product approval, it often makes business sense for a manufacturer to use more conventional technology for the product.<sup>63</sup> Furthermore, different requirements in other countries pose additional challenges to manufacturers that aspire to market a product internationally. While the National Academies of Sciences, Engineering, and Medicine report focused on pharmaceutical manufacturing, one expert we spoke to said the same principles apply to manufacturing for vaccines.

#### 4.4 Challenges affecting scaling up manufacturing to meet surges in demand

Two key challenges impact the ability to meet surges in vaccine demand, including surges caused by epidemics or global pandemics. The first is the capability of private sector manufacturers to meet new demand without negatively impacting their ability to manufacture other licensed vaccines. The second is the ability of the federal government to ensure that manufacturing capacity to respond to pandemics is available and operational.

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<sup>62</sup>Baxendale, I. R., R.D. Braatz, B. K.Hodnett, K. F. Jensen, M. D. Johnson, P. Sharratt, J-P. Sherlock, and A. J. Florence, "Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance," *Journal of Pharmaceutical Sciences*, vol. 104, no. 3, (2015): 781-791.

<sup>63</sup>National Academies of Sciences, Engineering, and Medicine, *Innovations in Pharmaceutical Manufacturing on the Horizon, Consensus Study Report Highlights*, National Academies Press (2021).

According to experts we spoke with, vaccine manufacturers cannot fully address novel threats from different categories of pathogens because they do not create excess, unused capacity for emergency events, and using existing infrastructure to manufacture pandemic vaccines could negatively impact the production of current vaccines for diseases such as measles, mumps, and rubella.

The federal government has attempted to address private sector capacity gaps by establishing manufacturing capacity and flexibility across a range of vaccine platforms to respond to infectious disease outbreaks. However, these attempts have not created adequate capacity to address real-world pandemic manufacturing needs.<sup>64</sup> For example, the Centers for Innovation in Advanced Development and Manufacturing have not been effectively maintained, updated, or made operationally ready to meet the new COVID-19 vaccine surge in manufacturing during the pandemic as noted by representatives from one center we spoke with and in congressional testimony.<sup>65</sup> Two key barriers inhibit scaling up manufacturing to meet such surges in demand.

- **Sufficiently trained personnel are limited.** For example, the COVID-19 vaccine cross contamination problems

at the Maryland center appeared to be due, in part, to inadequately trained personnel. Similarly, the Texas center found it challenging to fill open mid- and upper-management positions during COVID-19 vaccine ramp up.

- **Technologies and approaches that enhance flexibility or increase productivity are not supported.** For example, facility retrofitting and technology transfer of new manufacturing processes for COVID-19 vaccines required for the Texas and Maryland centers were done during the pandemic rather than in advance.

#### 4.5 Policy options that may help address challenges related to vaccine manufacturing

We identified two options for policymakers that may help address challenges related to the adoption of technologies and the improvement of vaccine manufacturing capacity and operational readiness. As mentioned previously, policymakers include Congress, federal agencies, state and local governments, academic and research institutions, and industry.

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<sup>64</sup>While the approximately 10.5 months it took to develop a COVID-19 vaccine was unprecedented, innovations and new approaches could accelerate vaccine development and manufacture in the future. For example, the Coalition for Epidemic Preparedness Innovations has an aspirational goal—“a moon-shot”—to make vaccines available in 100 days after determination of the pathogen’s genetic sequence.

<sup>65</sup>Transcript from “Examining Emergent Biosolutions’ Failure to Protect Public Health and Public Funds Hearing Before the Select Subcommittee On The Coronavirus Crisis of the Committee on Oversight and Reform House of Representatives One Hundred Seventeenth Congress First Session May 19, 2021.”



## Policy options that may help address challenges related to vaccine manufacturing

Policy option	Opportunities	Considerations
<p><b>Assess vaccine manufacturing capacity and operational readiness</b></p> <p><i>Policy makers could routinely assess U.S. manufacturing capacity and operational readiness.</i></p> <p>For example manufacturing capabilities could be pressure tested to determine the nation’s overall capability to manufacture current vaccines and meet pandemic surge demands.<sup>a</sup></p> <p>This could help address the challenges identified related to meeting new demands without negatively impacting manufacturers’ ability to produce current vaccines.</p>	<p>Determining U.S. vaccine manufacturing capacity and operational readiness and routinely pressure testing it can help identify gaps as well as key technologies and approaches to address them.</p>	<p>Vaccine manufacturing capacity requirements may change based on the specific infectious disease and vaccine platforms being pressure tested.</p>
<p><b>Improve preparedness</b></p> <p><i>Policy makers could provide support and coordination for public-private partnerships to strategically develop manufacturing capacity to respond to surge requirements.</i></p> <p>To maintain this capacity, partnerships could manufacture prototype vaccine candidates against high-priority pathogens.<sup>b</sup> For example, manufacturing, testing through phase 1-2 clinical trials, and stockpiling prototype vaccine candidates against prioritized classes of pathogens could decrease the amount of time needed to validate and scale up manufacturing processes if a pathogen from those classes does emerge.<sup>c</sup></p> <p>This could help address the challenges identified related to the ability of the federal government to ensure that the manufacturing capacity to respond to pandemics is available and operational.</p>	<p>Manufacturing, testing and stockpiling vaccine candidates could be mobilized in an emergency and more rapidly mitigate future pandemics.</p> <p>By leveraging strategic partnerships, policymakers could take steps to increase the availability of vaccines to more quickly address threats to the U.S. population.</p>	<p>May require new resources or reallocation of resources from other efforts.</p> <p>There may be a risk that the vaccines manufactured, tested, and stockpiled against prioritized pathogen classes miss certain pandemic pathogens.</p> <p>The stockpiled vaccines would need to be regularly replenished prior to expiration.</p>

Source: GAO. | GAO-22-104371

<sup>a</sup>Operational readiness includes having available, well maintained equipment and facilities as well as enough trained personnel. Further, operational readiness includes maintaining “warm” manufacturing capabilities—for example, by

operating at least one shift daily—so that equipment remains operational and personnel retain manufacturing competency.

<sup>b</sup>As described in chapter 2, if able to be developed and manufactured early in a pandemic, monoclonal antibody candidates may also provide some initial benefit.

<sup>c</sup>One expert estimated the cost to produce and test a vaccine through phase 2 clinical trials would be approximately \$50 million, with one-third of that cost required for manufacturing the vaccine.

## 5 Economics of vaccine development and the role of incentives

Vaccines confer significant public health and economic benefits. However, economists we spoke with stated that the benefits that vaccines provide are not necessarily commensurate with the return on investment from developing or manufacturing them. Experts attribute the low rate of vaccine investment to market failures (i.e., market interactions that fall short of what would have been socially beneficial), challenging markets for some vaccines, high costs, and risks of development. Experts also stated that uncertainty as to whether a vaccine, once developed, would be recommended for universal use—for example, for all children as opposed to a subset of individuals with certain risk factors—is an additional risk and negatively affects incentives to develop them as it reduces the number of people recommended to be vaccinated.<sup>66</sup>

Policymakers have a number of mechanisms to encourage investment in vaccine development. Some of these mechanisms have been used by HHS and the Department of Defense (DOD),

including funding for clinical trials, and offering a financial incentive for the successful development of vaccines for COVID-19. However, it is unclear whether policymakers have systematically examined how various tools can be used to incentivize vaccine investment.<sup>67</sup>

As discussed earlier, vaccines have far-reaching, positive effects on public health. In addition to health benefits, such as reducing death and preventing infectious diseases and certain types of cancer, vaccines also produce economic and social benefits. For example, a July 2020 report found that vaccination enhances economic growth due to improved health as well as productivity gains from better physical and cognitive performance.<sup>68</sup>

Vaccines also produce social benefits including improving equity in healthcare, increased life expectancy, and strengthening healthcare resources (see fig. 7). The July 2020 report also found that when infrastructure is developed to

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<sup>66</sup>One expert stated that vaccine entrants who enter a market first will have a larger market share. A 2014 report from McKinsey & Company found that first-to-market entrants into drug markets had a 6 percent market share advantage over later entrants. See M. Cha and F. Yu, “Pharma’s First To Market Advantage,” McKinsey & Company, Sept. 2014.

<sup>67</sup>Several entities have reported on large profits earned by pharmaceutical companies for COVID-19 vaccines. Economists we spoke to stated that, from a benefit-to-cost perspective, it makes sense for policymakers to invest significant funds in vaccine development, manufacturing capacity, and supply chain development to respond to an active pandemic to meet immediate needs and reduce loss of life. However, investing in vaccine technologies and manufacturing capacity in preparation for future pandemics has the potential to reduce costs for vaccines because these

capabilities will not have to be developed rapidly or all at once in response to a pandemic event. Similarly, having vaccine candidates under development for pathogens similar to a potential future pandemic pathogen may further reduce development costs as well as the overall price for vaccines. According to one economist we spoke to, investment undertaken at a more measured pace can be cheaper because it does not stretch scarce (and thus expensive) inputs. The economist noted that procuring vaccines under less urgency facilitates entry of multiple competitors and allows a competitive tender process to be organized that favors low prices over speed.

<sup>68</sup>C.M., Rodrigues and S.A., Plotkin, “Impact of Vaccines: Health, Economic and Social Perspectives”, *Frontiers in Microbiology*, vol. 11, article 1526 (2020): 1-15

**Figure 7: Types of benefits vaccines provide**

		
Health	Social	Economic
<ul style="list-style-type: none"> <li>• Improved life expectancy and reduced morbidity</li> <li>• Herd immunity or eradication of infectious disease</li> <li>• Lower healthcare costs</li> <li>• More resilient health care systems</li> </ul>	<ul style="list-style-type: none"> <li>• More equal distribution of health outcomes and opportunity</li> <li>• Enhanced social mobility through better health</li> <li>• Strengthening social care infrastructure concurrent with improved health care infrastructure</li> </ul>	<ul style="list-style-type: none"> <li>• Productivity gains resulting from a larger and more productive workforce</li> <li>• Increased lifetime productivity from better health</li> <li>• Strengthened family, community, and economic outcomes</li> <li>• Increased gross domestic product</li> </ul>

Source: GAO analysis and literature; Vectorfair.com/RealVector/dlyastokiv/stock.adobe.com. | GAO-22-104371

administer vaccines, it provides a basis for the provision of other health and social care services, particularly improving maternal and infant mortality in developing regions. Although making projections about the economic and social benefit of vaccines is complex, a 2005 economic article reported that current childhood vaccinations against tetanus, polio, measles, mumps, rubella, hepatitis B, and others, when considered together, create significant economic and social benefits.<sup>69</sup>

### 5.1 Market failures and other challenges result in fewer vaccines

Market failures occur when interactions in the market lead to outcomes that fall short

of what would have been socially beneficial. In the case of vaccines, market failures lead to vaccine developers producing fewer vaccines than what would have most benefited society, resulting in less protection from infectious diseases. Other challenges that contribute to low vaccine investment include markets that offer no or negative returns on investment, as well as the high cost and low probability of success in developing vaccines.

#### 5.1.1 Positive externalities

We focused on two specific market failures for vaccine development.<sup>70</sup> The first has to do with the nature of vaccines. Vaccines offer protection to those who are

<sup>69</sup> Current childhood vaccines against diphtheria, tetanus, pertussis, Hib, polio, measles, mumps, rubella, and hepatitis B, when considered together, were estimated to have a benefit cost ration of more than five to one for direct costs and seventeen to one for societal costs. T.A. Lieu, et al.,

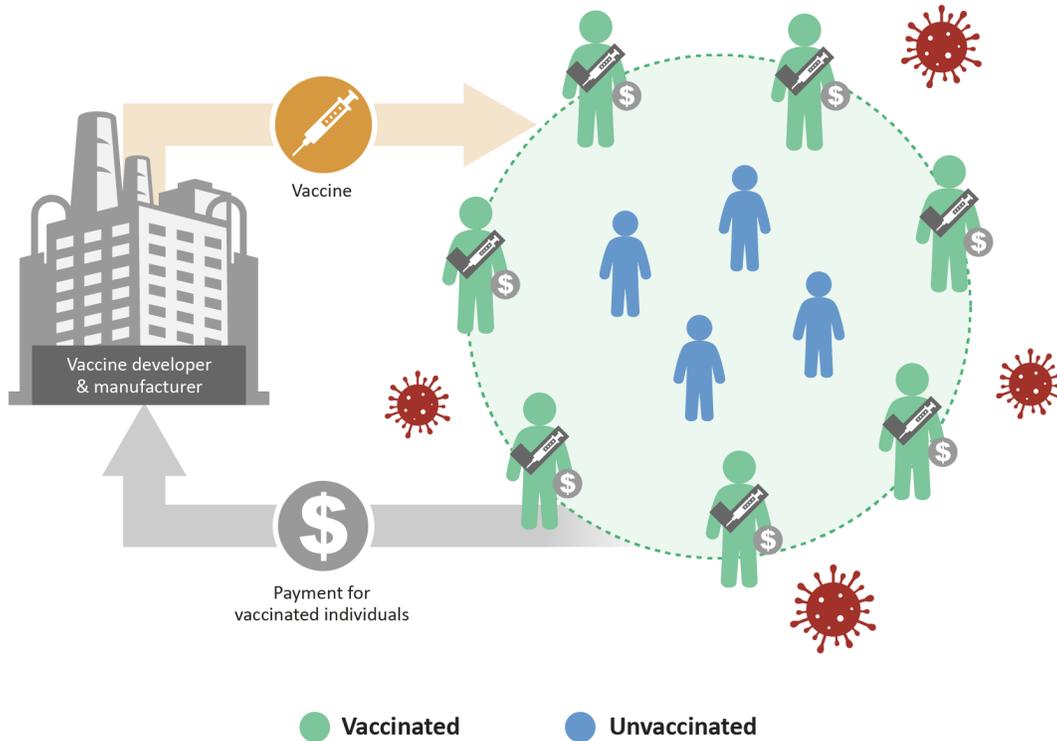
“Overcoming Economic Barriers to the Optimal Use of Vaccines,” *Health Affairs*, vol. 24, no. 3 (2005): 667.

<sup>70</sup> Other market failures may also explain underinvestment in vaccines. For example, vaccine research is a “public good” as the benefits of scientific and technological advances can extend to others, regardless of who is making the

vaccinated as well as providing some level of protection to those who are not by reducing the spread of infectious disease (see fig. 8). In economics, this situation is known as a positive externality. Because this protection is inherent to all vaccines, developers are unable to price their

products based on this additional benefit and, as a result, are not rewarded for preventing the spread of the disease. Consequently, developers tend to underinvest in vaccines, even though society would benefit from having more vaccines available.

**Figure 8: Vaccines provide some level of protection for individuals who are unvaccinated**



Source: GAO analysis and Maksim/martialred/Nizwa Design/dlyastokiv/stock.adobe.com. | GAO-22-104371

Note: This figure is not intended to demonstrate vaccination levels commensurate with herd immunity. For more information on herd immunity, see [GAO-20-646SP](#).

investment, without reducing anyone else's access to the advances. Researchers and developers cannot fully capture the financial benefits of this research and tend to invest less than what the social value of this knowledge is, leading to a situation where government action can improve upon market outcomes. Similarly, one economist we spoke to stated that there is a market failure associated with

developers being limited in how much they can charge when a pandemic arises. In this situation, the price is not set by the market but by government purchases, and governments can limit prices, which means that the developers' expected revenue is low.

### 5.1.2 Imperfect information

The second type of market failure is caused by the inability of developers to fully account for the disease risk in the price of the product because of imperfect information. Vaccine developers have little information on how likely a particular healthy person is to contract the disease or seek vaccination to avoid becoming sick. However, when an individual contracts the disease, the developer knows that the individual is likely to seek treatment.<sup>71</sup> Developers can use this information to charge much higher prices for therapeutics than vaccines. As a result, the return on investment from vaccines is commonly lower than that of therapeutics. With price incentives skewed away from vaccines and toward therapeutics, vaccines make up only about 1.5 percent of global pharmaceutical sales.<sup>72</sup>

In an example of a disease where workers employed in an industry may be at higher risk of being infected than workers not in that industry, workers in that industry who are at higher risk would be willing to pay a higher price for a vaccine. Workers not in that industry who are less likely to become infected would not be willing to pay as much. However, all workers could become infected and suffer adverse health consequences. If the vaccine's price was too

high, only workers in the industry would choose to get vaccinated, leaving others unprotected. If a significant portion of the market—in this case, workers not in the industry—chose not to purchase the vaccine because of its price, then the developer would have less incentive to produce the vaccine.

### 5.1.3 Challenging markets due to uncertain demand

Some markets offer little, no, or negative returns on investment, presenting challenges to vaccine developers. Such markets include vaccines that are developed for infectious diseases that occur only in developing countries, are considered low priority, or may result in future pandemics but are not currently an issue.<sup>73</sup> Experts told us that because of low returns or uncertainty in these markets, developers have little financial incentive to invest in such vaccines.

Experts stated that infectious diseases that primarily affect developing countries which have little ability to pay for vaccines provide little incentive for investment. For example, a May 2020 study estimated that the rate of investment return on a portfolio of vaccines for nine infectious diseases identified by the Coalition for Epidemic Preparedness Innovations as high priority, many of which

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<sup>71</sup>The developer may have some information about the probability distribution of a particular infectious disease in the population. However, an individual's likelihood of contracting the disease depends on many other factors including the individual's behavior and the availability and use of preventive measures, which are unknown to vaccine developers. In the case of therapeutics, the developer can indirectly observe who has contracted the disease by observing who seeks treatment for it.

<sup>72</sup>T.A. Lieu, et al., "Overcoming Economic Barriers." 675.

<sup>73</sup>NIAID officials stated that it conducts research to develop vaccine candidates that is not subject to the same market challenges that private sector developer's face.

affect developing countries, was negative 61 percent, implying that the private sector is unlikely to address this need without public-sector intervention.<sup>74</sup> In these instances, international organizations, such as the Coalition for Epidemic Preparedness Innovations and philanthropic entities such as the Bill and Melinda Gates Foundation fund research in these infectious diseases.<sup>75</sup> (See textbox for an example of a challenging market).

**Challenging Market for Group A *Streptococcus* Vaccine**

Group A *Streptococcus* causes, among other things, strep throat, scarlet fever, and rheumatic fever. Currently, there is no vaccine, even though about 500,000 people worldwide die due to Group A *Streptococcus* infections annually, including between 1,100 and 1,600 deaths in the U.S. The pathogen is one of the top 10 causes of death from infectious diseases worldwide and is considered endemic in lower income areas of the globe. While NIAID supports research to develop a vaccine with several candidates in various phases of development, one expert told us that to produce a Group A *Streptococcus* vaccine at a price that could be purchased in lower income countries (less than \$2 per dose), a business case analysis anticipated that total sales would be between \$200 million and \$300 million annually, which is not sufficient to incentivize developers to invest in such a vaccine.

Source: GAO analysis of information from literature and an expert meeting. | GAO-22-104371

Further, infectious diseases that are considered lower priority can have limited market potential. For example, one expert

told us that Epstein-Barr virus, which can cause mononucleosis rarely results in death, and therefore is considered a low priority for vaccine development.<sup>76</sup> Another expert stated that companies would be more encouraged to develop a vaccine for a larger or more defined population, such as children or people over the age of 65. For example, CDC recommends that all individuals 50 years or older should receive the vaccine for shingles.

Vaccines for pathogens that may cause future pandemics but are not currently a significant issue also face uncertain market demand. Because developers receive no return on their investment unless a pandemic occurs, there is little incentive to invest in these vaccines. Further, even if a pandemic event does occur, the demand for a vaccine may still be uncertain. If an outbreak quickly dissipates, the market for the vaccine may be limited because individuals may not seek a vaccine and governments may be unlikely to purchase it. For example, a May 2020 report found that the SARS and Zika epidemics ended before vaccine development was complete, and federal funding agencies reallocated funds that had been committed to vaccine development for these diseases, leaving manufacturers with financial losses and

<sup>74</sup>The study estimated a rate of return for a portfolio of 141 trial vaccines to address infectious diseases from the Coalition for Epidemic Preparedness Innovations' Priority Pathogen List including: Chikungunya, MERS, SARS, Marburg, Rift Valley Fever, Lassa, Nipah, Crimean-Congo hemorrhagic Fever, and Zika virus. See J. Vu et al., "Financing Vaccines for Global Health Security," *National Bureau of Economic Research*, May 2020.

<sup>75</sup>The Bill and Melinda Gates Foundation is a philanthropic organization that funds global health efforts. A priority area for the Gates Foundation is to develop effective and affordable vaccines, medicines, and other health tools.

<sup>76</sup>According to CDC, Epstein-Barr virus is one of the most common human viruses in the world. It spreads primarily through saliva. Epstein-Barr virus can cause infectious mononucleosis, also called mono, and other illnesses. Most people will get infected with Epstein-Barr virus in their lifetime and will not have any symptoms. Mono caused by Epstein-Barr virus is most common among teens and adults. Other infections sometimes go along with mononucleosis, which may need to be treated with antibiotics. NIH noted that its researchers have developed vaccine candidates for Epstein-Barr virus. For more information see <https://www.cdc.gov/epstein-barr/index.html>.

setting back other vaccine development programs.<sup>77</sup> The article also found that, even with successful development and licensure, commercial markets still may not sustain multiple vaccines for which relatively few doses may need to be manufactured. One expert said that the potentially low number of doses to be manufactured increases the uncertainty of the potential return on investment and therefore risk for vaccine developers, which creates an even lower incentive to develop a vaccine during any subsequent infectious disease outbreak and hinders preparation for future pandemics.

Another expert told us that vaccines placed on vaccine schedules—the lists of vaccines recommended for children and adults in the U.S.—and recommended for universal use generally have large markets and are often covered by insurance. However, the lack of assurance that a vaccine would be considered for inclusion on the vaccine schedule can also hinder investment. For example, experts told us that, following review by the CDC’s Advisory Committee on Immunization Practices, a vaccine for meningitis B was not recommended for universal use.<sup>78</sup> This recommendation

effectively reduced the number of people who would be receiving the vaccine and, therefore, the return on investment.<sup>79</sup>

#### 5.1.4 High development costs and low probability of success

Two additional challenges further contribute to the low return on investment: high costs and low probability of success.<sup>80</sup>

- **High costs.** According to a 2018 study, vaccine development from discovery to licensure can cost billions of dollars and can take over 10 years to complete.<sup>81</sup>
- **Low probability of success.** The same study found that on average, vaccine candidates have a 94 percent chance of failure.

### 5.2 Mechanisms to incentivize vaccine development

Several mechanisms can potentially be used to incentivize additional investment in vaccines. These mechanisms either subsidize some portion of the development process or provide rewards for successful development. Given the market failure

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<sup>77</sup>See N. Lurie, et al., “Developing COVID-19 Vaccines at Pandemic Speed,” *The New England Journal of Medicine*, vol. 382, no. 21 (2020): 1969

<sup>78</sup>CDC’s Advisory Committee on Immunization Practices is comprised of medical and public health experts who make recommendations on the use of vaccines in the civilian population of the U.S. Its recommendations serve as public health guidance for safe use of vaccines and other related products. If adopted by the CDC Director, CDC’s Advisory Committee on Immunization Practices’ recommendations are published as official HHS/CDC recommendations in the *Morbidity and Mortality Weekly Report*.

<sup>79</sup>According to CDC, in 2019, there were about 371 total cases of meningococcal disease reported. CDC recommends

that adolescents between the ages of 16 and 23 consult with their clinician to determine whether they should receive the vaccine.

<sup>80</sup>One economist we spoke to stated that some factors impair how lucrative a market is, but they aren’t market failures if they don’t generate a wedge between a firm’s commercial incentives and social benefits. Factors, such as high cost and low probability of success are not market failures, but they may serve to amplify them.

<sup>81</sup>D. Gouglas et al., “Estimating the Cost of Vaccine Development Against Epidemic Infectious Diseases: a Cost Minimisation Study,” *The Lancet Global Health*, vol. 6, no. 12 (2018): pp. e1386-e1396.

associated with vaccines, it is unlikely private investments will sufficiently support the development of all socially beneficial vaccines. Policymakers could fill this gap by taking actions to incentivize investment in new vaccines to better address infectious disease; improve overall societal, health, and economic outcomes; and prepare for future pandemics. To do so, policymakers need a combination of tools to incentivize investment. HHS has leveraged some mechanisms to incentivize vaccine investment, most recently to respond to the COVID-19 pandemic.

### 5.2.1 Incentives for vaccine investment

We identified several mechanisms with the potential to incentivize vaccine investment. According to experts, policymakers need access to a wide range of mechanisms, because different mechanisms are better for some infectious disease scenarios than for others.

Policymaker interventions can be broadly classified into push and pull incentives (see table 4). Push incentives subsidize the costs of developing a product or general research in vaccines by providing funding for grants to academic institutions, tax credits for R&D, and low or no cost manufacturing. Pull incentives increase revenue once a vaccine receives authorization or licensure. This can be done, for example, by guaranteeing to purchase a certain quantity or promising a cash prize for successful authorization or licensure. Other examples of pull incentives include patent extensions and priority review vouchers (which can be sold for revenue or used for faster review on a future drug or biologic application).

**Table 4: Potential mechanisms to incentivize vaccine development**

Mechanism	Definition	Opportunities	Challenges
Grants (push)	Financial assistance that may cover some or all of the costs associated with vaccine R&D	<ul style="list-style-type: none"> <li>Support basic research that cannot be incentivized with pull funding</li> </ul>	<ul style="list-style-type: none"> <li>Do not guarantee development of a product</li> </ul>
Tax incentives (push)	Reductions in tax liabilities to defray some of the costs of R&D	<ul style="list-style-type: none"> <li>Support basic research that cannot be incentivized with pull funding</li> </ul>	<ul style="list-style-type: none"> <li>Do not guarantee development of a product</li> <li>Can be very costly</li> <li>Beneficial only if the developer has a tax liability</li> </ul>
Advanced purchase commitments (pull)	Agreements to purchase vaccines in the future, after they are fully developed	<ul style="list-style-type: none"> <li>Product can be stockpiled for future use or used to vaccinate people immediately, or both</li> <li>In many cases, paid only if a product is developed and receives emergency use authorization or licensure</li> <li>Developers can be incentivized to select the most promising products</li> </ul>	<ul style="list-style-type: none"> <li>Can be expensive, especially if several products are incentivized</li> </ul>
Subsidizing manufacturing capacity (push)	Allowing excess manufacturing capacity to be used to manufacture vaccines for clinical trials at low or no cost	<ul style="list-style-type: none"> <li>Developers can be incentivized to take vaccines to clinical trials due to lower manufacturing costs</li> <li>Excess capacity can be used to respond to future infectious disease outbreaks</li> </ul>	<ul style="list-style-type: none"> <li>May be expensive to maintain facilities for manufacturing</li> <li>May not ensure sufficient capacity to respond to all potential infectious diseases scenarios</li> </ul>
Prizes (pull)	Reward for receiving authorization or licensure of a vaccine product	<ul style="list-style-type: none"> <li>Product can be stockpiled for future use, used to vaccinate people immediately, or both</li> <li>In many cases, paid only if a product is developed and receives emergency use authorization or licensure</li> </ul>	<ul style="list-style-type: none"> <li>Do not reduce the cost of R&amp;D</li> <li>Would have to be sufficiently large to induce investment</li> </ul>
Patent extensions (pull)	An extension on a patent that exceeds the usual time limits	<ul style="list-style-type: none"> <li>Greater protection from competition and a longer period to benefit from higher prices may encourage greater innovation</li> </ul>	<ul style="list-style-type: none"> <li>Patents can result in higher prices, making the vaccine too expensive for some patients or governments</li> </ul>
Priority review voucher (pull)	Award for the development of drugs and biologics,	<ul style="list-style-type: none"> <li>Potential for additional revenue could provide an incentive to develop</li> </ul>	<ul style="list-style-type: none"> <li>The financial reward—that is, the amount of revenue earned from sale of a priority review</li> </ul>

including vaccines, for tropical diseases, rare pediatric diseases, and material threat medical countermeasures, which can be sold or redeemed for faster review of a future application.	vaccines for tropical diseases, rare pediatric diseases, and medical countermeasures	voucher—could decline if more vouchers are awarded and available for sale
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Source: GAO. | [GAO-22-104371](#)

Experts we spoke to stated that different incentives work better for developing vaccines for some infectious diseases than for others. For example, push incentives such as grants, may be beneficial because they can encourage the use of a particular technology, such as certain vaccine platforms. However, grants do not necessarily result in the development of a vaccine. Tax incentives may be useful in incentivizing research into a particular area, but they do not work for developers without tax liability. Similarly, offering unused manufacturing capacity, public or private, for no or low cost to vaccine developers to produce vaccine candidates for clinical trials can encourage developers to proceed with testing of candidates that they might not have been able to otherwise. This mechanism also has the benefit of keeping manufacturing capacity “warm” (i.e., available and ready to be used) and personnel at these facilities trained so they can quickly respond to potential pandemics. One expert told us that the cost to move a vaccine candidate through phase 2 clinical trials is about \$50 million, with one third of that cost spent on manufacturing vaccines in support of the trials.

Pull incentives also have opportunities and challenges. Advanced market commitments are most beneficial when a vaccine will be

administered to a large number of people, such as the entire population of a country. However, when a vaccine will be used by a smaller number of people, such as during a regional epidemic, the number of doses of the vaccine to be purchased may not be enough of an incentive. In these instances, a prize may be more appropriate. One benefit of pull incentives is that, in many cases, developers are only paid if a vaccine is eventually produced and is authorized for emergency use or licensed.

Pull funding is intended to supplement, not replace, push funding. For example, pull incentives may not incentivize sufficient at-risk manufacturing capacity for developers, leading to fewer vaccines than would have been beneficial from society’s perspective. A combination of pull and push funding may be needed to assure sufficient vaccine supply can be manufactured. Additionally, a combination of push and pull incentives may allow for program costs to be lower than with pull incentives alone, while avoiding some of the inefficiency created by push incentives.

Experts we spoke to stated that the best mechanisms to incentivize vaccine investment would:

- Reward the development of new vaccines
- Keep prices low and thus allow vaccines to be accessible to as many people as possible
- Incentivize several pharmaceutical companies to produce vaccines by allowing benefits from incentives to be available to all pharmaceutical companies, not just some
- Be simple
- Be transparent to operate
- Develop a capacity that allows for better responses to endemic infectious diseases as well as prepare for potential future epidemics or pandemics

### 5.2.2 Federal use of vaccine incentives

Some HHS programs have incentivized the development of vaccines. For example, the priority review voucher programs are intended to encourage development of drugs or biologics for tropical diseases, rare pediatric diseases, and material threat medical countermeasures.<sup>82</sup> If an application meets the criteria for one of the

priority review voucher programs, FDA can award a voucher upon approval of the application.<sup>83</sup> These vouchers may be redeemed with submission of a future application, shortening FDA's targeted review time from the standard 10-month review to 6 months.<sup>84</sup> The vouchers may also be sold or transferred to another company, which may then choose to use it or similarly sell or transfer it.

A partnership between HHS and DOD was established in May 2020 to accelerate the development, manufacturing, and distribution of COVID-19 vaccines.<sup>85</sup> This was accomplished through the award of contracts and other transaction agreements to six vaccine companies for different types of activities, including clinical development and manufacturing activities or the purchase of COVID-19 vaccine doses. These awards were made, according to HHS and DOD officials, in anticipation that some of the vaccine candidates would subsequently receive authorization or licensure. By providing significant up-front funding to several of the companies, the government took on some financial risk, which enabled these companies to accelerate vaccine development and production.<sup>86</sup> As of

<sup>82</sup>See 21 U.S.C. §§ 360n (tropical diseases), 360ff (rare pediatric diseases), and 360bbb-4a (material threat medical countermeasures). Material threat medical countermeasures are drugs and biologics used to prevent or treat harm from any chemical, biological, radiological, and nuclear agent identified as a material threat.

<sup>83</sup>From 2009 through 2019, FDA awarded 31 priority review vouchers to drug sponsors. Of those, available data indicate that 17 were subsequently sold to another drug sponsor, providing revenue to the sponsor selling the priority review voucher. See GAO, *Drug Development, FDA's Priority Review Voucher Programs*, GAO-20-251 (Washington, D.C.: Jan. 31, 2020).

<sup>84</sup>For new drugs that do not contain a new molecular entity, FDA's goal is to review and act on 90 percent of standard

applications within 10 months and 90 percent of priority applications within 6 months of receipt. For original biologics and new drugs that contain a new molecular entity, FDA's goal is to review and act on 90 percent of standard applications within 10 months following a 60-day filing period (a total of 12 months from receipt). Priority review reduces this time to 6 months following the filing period (a total of 8 months from receipt).

<sup>85</sup>This partnership was formerly known as Operation Warp Speed, but since May 2021 it has been called the HHS-DOD COVID-19 Countermeasures Acceleration Group.

<sup>86</sup>See, *COVID-19: Efforts to Increase Vaccine Availability and Perspectives on Implementation*, GAO-21-443, (Washington, D.C.: Apr. 14, 2021).

October 2021, three COVID-19 vaccines that participated in the federal partnership were available in the U.S.

While HHS has used some mechanisms intended to incentivize development, it is not clear that it has examined how or under what circumstances different incentives can be most effective. In June 2021, BARDA officials told us that they were not aware of any HHS effort to examine market incentives for vaccines.

Further, experts we spoke with expressed concern that, if policymakers do not have the authority to implement appropriate incentives, they will be limited in their ability to help facilitate investment in new vaccines. If officials lack the authority to use different mechanisms, it may result in reduced preparation for future pandemics and weakened efforts to address infectious disease.

### **5.3 Policy options that may help address economic challenges to vaccine development**

We identified three policy options for policymakers that may help address economic challenges with incentivizing vaccine development. As mentioned previously, policymakers include Congress, federal agencies, state and local governments, academic and research institutions, and industry.

Policymakers could conduct a systematic assessment of the various mechanisms to incentivize vaccine development to determine which incentives could work best for infectious diseases identified as high priority, as discussed in chapter 2. Policymakers could also examine the authorities necessary to use these mechanisms and, to the extent that agencies lack such authority, take steps to obtain or provide it.



**Policy options that may help address economic challenges related to vaccine development**

<b>Policy option</b>	<b>Opportunities</b>	<b>Considerations</b>
<p><b>Evaluate factors that discourage vaccine investment</b></p> <p><i> Policymakers could collaborate across sectors, such as government, academia and industry, to conduct a systematic evaluation of factors that discourage developers from investing in new vaccines.</i></p> <p>This could help address the challenges we identified related to market failures, challenging markets, high costs, and low probability of success.</p>	<p>A clear understanding of the range of factors discouraging vaccine investment would provide the basis for effectively addressing those factors.</p>	<p>Collaboration between policymakers and other stakeholders to obtain all relevant viewpoints can be time-consuming and it may be hard to reach a consensus.</p>
<p><b>Evaluate mechanisms for increasing vaccine investment</b></p> <p><i> Policymakers could consider conducting a systematic evaluation of the effectiveness of different mechanisms to incentivize vaccine investment and determine what circumstances or time frames may make some mechanisms more or less useful.</i></p> <p>For example, policymakers could evaluate the effectiveness of mechanisms used to incentivize COVID-19 vaccine development.</p> <p>This could help identify when mechanisms to incentivize vaccine development is likely to be most successful.</p>	<p>Economic and societal costs from infectious diseases could be reduced.</p>	<p>Evidence on some mechanisms for incentivizing vaccine investment may not be available or sufficient to make determinations on the effectiveness of some mechanisms.</p>
<p><b>Evaluate authority</b></p> <p><i> Policymakers could consider determining whether HHS, DOD, or other relevant agencies have the authority to use these mechanisms to incentivize vaccine development. For any identified gaps in authority, policymakers could consider seeking or providing such authority.</i></p> <p>This could help address the challenges we identified related to incentivizing vaccine development.</p>	<p>Identifying and addressing any gaps in authority could allow policymakers to more effectively address the economic challenges to vaccine development.</p>	<p>Granting additional authority may not result in increased use of these mechanisms to address economic challenges.</p> <p>Even if incentives are used more widely, additional vaccines may not be produced due to technical and other challenges.</p> <p>Expanded use of incentives is likely to require more resources or a shifting of resources from other areas.</p>

Source: GAO. | [GAO-22-104371](#)

## 6 Agency and Expert Comments

We provided a draft of this product to DOD and HHS for review. DOD concurred without comment with the draft report provided by GAO. HHS provided technical comments on the draft report, which we incorporated as appropriate. Nine participants from our expert meeting also reviewed a draft of this product; we incorporated their technical comments as appropriate.

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We are sending copies of this report to the appropriate congressional committees and other interested parties. In addition, the report is available at no charge on the GAO website at <https://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-6888 or [howardk@gao.gov](mailto:howardk@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix VI.



Karen L. Howard, PhD  
Director,  
Science, Technology Assessment, and Analytics

## ***List of Congressional Addressees***

**The Honorable Patrick Leahy**

Chairman

**The Honorable Richard Shelby**

Vice Chairman

Committee on Appropriations

United States Senate

**The Honorable Ron Wyden**

Chairman

**The Honorable Mike Crapo**

Ranking Member

Committee on Finance

United States Senate

**The Honorable Patty Murray**

Chair

**The Honorable Richard Burr**

Ranking Member

Committee on Health, Education, Labor,  
and Pensions

United States Senate

**The Honorable Gary C. Peters**

Chairman

**The Honorable Rob Portman**

Ranking Member

Committee on Homeland Security and  
Governmental Affairs

United States Senate

**The Honorable Rosa L. DeLauro**

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**The Honorable Kay Granger**

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Committee on Appropriations

House of Representatives

**The Honorable Frank Pallone, Jr.**

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**The Honorable Cathy McMorris Rodgers**

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Committee on Energy and Commerce

House of Representatives

**The Honorable Bennie G. Thompson**

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**The Honorable John Katko**

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Committee on Homeland Security

House of Representatives

**The Honorable Carolyn B. Maloney**

Chairwoman

**The Honorable James Comer**

Ranking Member

Committee on Oversight and Reform

House of Representatives

**The Honorable Richard Neal**

Chairman

**The Honorable Kevin Brady**

Republican Leader

Committee on Ways and Means

House of Representatives

## Appendix I: Objectives, Scope, and Methodology

### Objectives

This report identifies and discusses:

1. technologies and approaches for vaccine research and development (R&D) and challenges that affect their use,
2. technologies and approaches for vaccine testing and challenges that affect their use,
3. technologies and approaches for vaccine manufacturing and challenges that affect their use, and
4. economic factors that affect vaccine investment and preparedness for future pandemics

### Scope and methodology

To address the first three of our objectives, we assessed available and developing technologies and approaches that vaccine developers could use for R&D, testing, and manufacturing of vaccines. For the fourth objective, we assessed available and potential mechanisms for incentivizing vaccine development. To do so, we reviewed scientific literature describing current and developing tools; interviewed experts from government, academia, the nonprofit sector, and the research industry; and collaborated with the National Academies of Sciences, Engineering, and Medicine to convene a 3-day expert meeting to discuss the objective topics.

### Limitations to scope

We focused our assessment on U.S. vaccine development. However, with pandemics posing a global threat, the policy options we identified include actions U.S. policymakers can take alongside international partners. The technologies and approaches to vaccine development, testing, and manufacturing discussed in this report are not an exhaustive list of all possible methods. We selected technologies and approaches we identified as most promising from our review of the literature and from discussions with stakeholders. We do not discuss technologies and approaches related to how vaccines are distributed after they have been manufactured, as that was not within our scope. The list of mechanisms for incentivizing vaccine investment are also not exhaustive of all possible methods.

### Literature search

In the course of our work we conducted literature searches with ProQuest using search terms including “vaccine technology,” “clinical trials,” “vaccine manufacturing,” and “vaccine economics,” among a wide selection of keywords relevant to vaccine research and development. We conducted a broad search of materials published within the last 7 years, including scholarly articles and government reports. We used the results of our literature review to address our objectives as well as identify experts to interview and to participate in our expert meeting.

## Interviews

We interviewed stakeholders and experts with a diverse set of perspectives on the science, administration, and economics of vaccine development.

To address technologies, and approaches for vaccine R&D, we discussed developments in vaccine platforms and ways researchers can identify and characterize pathogens and antigens. To address vaccine testing we discussed the design and purpose of preclinical testing, clinical trials, and ways vaccine testing could be conducted more efficiently and effectively. For manufacturing, we discussed emerging vaccine manufacturing technologies and infrastructure approaches to support greater flexibility, productivity, and capacity. To address the economic landscape of vaccine development, we discussed the market for vaccines as compared to other pharmaceutical products, the development costs and time requirements of vaccines relevant to other products, how these factors influence the choices made by pharmaceutical companies in deciding whether to develop vaccines, and government efforts to encourage vaccine development. For all relevant objectives, we spoke with stakeholders about key issues affecting the adoption of the technologies and approaches we identified.

## Expert meeting

To address all of our objectives, we held an expert meeting from January 25-28, 2021. This meeting was held in collaboration with the National Academies of Sciences, Engineering, and Medicine and was divided into six sessions, each moderated by two or three representatives from GAO.<sup>87</sup> The topics of each session were: (1) Technologies and Approaches for Research and Development, (2) Technologies and Approaches for Vaccine Manufacturing, (3) Technologies and Approaches for Preclinical Studies and Clinical Trials, (4) Pathogen Scenarios, (5) Economic Factors that Impact Vaccine Investment, (6) Lessons Learned and Next Steps.

Meeting participants were selected if they had expertise either broadly or specifically in at least one area related to our four objectives. We provided the National Academies of Sciences, Engineering, and Medicine with descriptions of the expertise needed by expert meeting participants. From this information, the National Academies provided an initial list of experts to potentially participate in the expert meeting. We reviewed the list and provided an additional list of experts based on our review of the literature. In addition to evaluating experts on the basis of their expertise, we evaluated them for any conflicts of interest. A conflict of interest was considered to be any current financial or other interest, such as an organizational position, that might conflict

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<sup>87</sup>This meeting of experts was planned and convened with the assistance of the National Academies of Sciences, Engineering, and Medicine to better ensure that a breadth of expertise was brought to bear in its preparation. However all final decisions regarding meeting substance and expert participation were made by GAO.

with the service of an individual because it could (1) impair objectivity or (2) create an unfair competitive advantage for any person or organization. Of the 22 experts, some were affiliated with companies, government, or research-funding entities. We took these affiliations into consideration as potential conflicts of interest when conducting our analysis and preparing our report. We determined that these experts' relationships did not account for any inappropriate biases in our reporting. We did not suggest policy options that we have reason to believe will improperly promote or adversely affect any company. The comments of these experts generally represented the views of the experts themselves and not the agency, university, or company with which they were affiliated, and are not generalizable to the views of others in the field. Appendix V provides additional information on the meeting participants.

### *Policy options*

Based on our research, we developed a series of policy options. Policy options are not formal recommendations for federal agencies, or matters for congressional consideration, but they are intended to represent possible options policymakers can take to address a policy objective.<sup>88</sup> For each policy option we discussed potential opportunities and considerations. These are not listed in any particular order within each chapter, nor are they inclusive of all possible policy options.

Based on the goal of improving U.S. vaccine development capabilities, we decided on an objective designed to identify options that could help improve capabilities for developing vaccines more effectively and efficiently, including during emergencies. We limited policy options to those that fit the objective and fell within the report scope.

To develop the policy options, we compiled a list of possible options (19 in total) over the course of our work based on our review of the scientific and economic literature, interviews with experts, and our vaccine development expert meeting. We analyzed these options and removed ideas that were either redundant, not feasible to implement, or did not fit into the overall scope of our work. We then analyzed each policy option by identifying potential benefits and considerations of implementing them. The policy options and analyses were supported by documentary and testimonial evidence.

We conducted our work from June 2020 to November 2021 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

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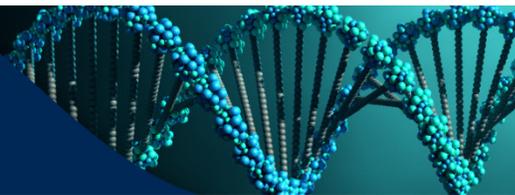
<sup>88</sup>Policymakers is a broad term including, for example, Congress, federal agencies, state and local governments, academic and research institutions, and industry.

## Appendix II: Research and Development Technologies and Approaches

We identified four technologies and approaches that may improve vaccine research and development (R&D). This appendix provides three summaries of these technologies and approaches. Additionally, this appendix provides a summary of monoclonal antibodies, which are emerging as an important approach to preventing infectious disease.

These summaries are based on documents we reviewed and interviews we conducted. Specifically, we reviewed scientific literature describing current and developing tools, interviewed experts from government, academia, the nonprofit sector, and industry, and collaborated with the National Academies of Sciences, Engineering, and Medicine to convene a 3-day expert meeting to discuss these technologies and approaches. Each summary includes information on what the technology or approach is, its maturity, and how it works.

# Omics and Reverse Vaccinology

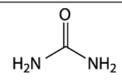


By integrating information from multiple fields of biology—collectively known as omics and including fields such as genomics and proteomics— researchers can better understand how pathogens cause illness and how different people respond to immunization. Reverse vaccinology applies omics approaches to identify potential vaccine candidates more effectively and shorten development time. In the future, such approaches could lead to a new generation of vaccines that are safer, generate a stronger immune response, and perhaps can even be personalized for vulnerable populations.

## What is it?

Omics refers to the combined study of multiple areas of biology whose names end with “omics.” The omics commonly used in vaccine development include genomics, transcriptomics, proteomics, and metabolomics (table 1).

**Table 1: Some omic fields used in vaccine development**

Field	Description
 Genomics	Genomics is the study of the genome—the complete set of genetic instructions to create an organism. Studying the genome is the first step in reverse vaccinology and allows researchers to understand what information exists and, therefore, what could happen inside microbial organisms or human cells.
 Transcriptomics	Transcriptomics is the study of RNA. RNA carries genetic instructions on what proteins should be made by the cells. Studying RNA allows researchers to understand what genetic information is being used and, therefore, what appears to be happening inside microbial organisms or human cells.
 Proteomics	Proteomics is the study of the proteins made within a microbial organism or human cell. Proteins play leading roles in cellular structure, facilitating metabolic reactions, and responding to stimuli, among other things. Studying proteins allows researchers to more directly observe cellular processes.
 Metabolomics	Metabolomics is the study of small molecules, commonly known as metabolites, made within a microbial organism or human cell. Metabolites can be found in biological samples, such as saliva, blood, and urine. Studying metabolites allows researchers to understand what is or has happened within a microbial organism or human cell.

Source: GAO analysis and fizzaig/ logos2012/stock.adobe.com. | GAO-22-104371

Reverse vaccinology analyzes a pathogen’s genome to identify the individual genes that are most likely to provide instructions for proteins that stimulate an immune response (antigens). This approach differs from traditional methods where the first step is to grow pathogens in a lab and characterize multiple antigens over many iterations.

Source: Design Cells/stock.adobe.com (header). | GAO-22-104371

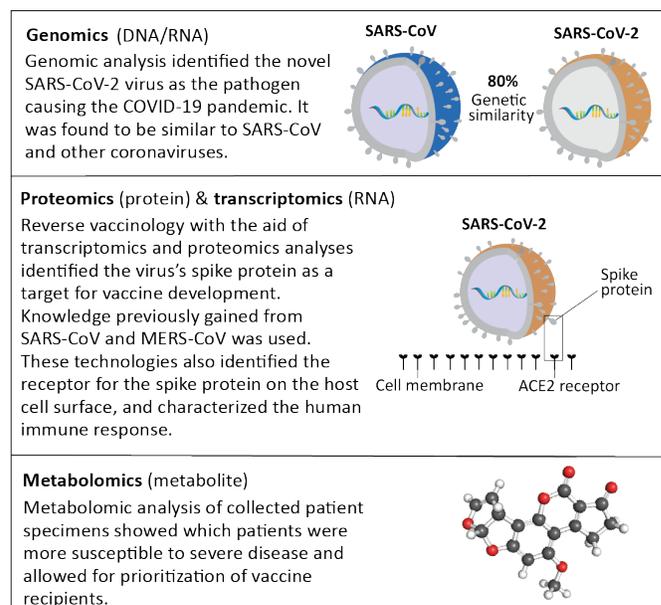
## How mature is it?

Individually, these omics fields are not new. However, recent advances in technology have allowed for integrated analyses that apply a combination of omics across large datasets, resulting in much faster development of vaccines, including those for COVID-19 (10 months to develop) and Ebola virus (5 years).

## How does it work?

Within a cell, information generally flows from the genome (DNA) to proteins and metabolites via RNA. Researchers can use omics and reverse vaccinology to identify antigens faster and compare antigens to identify similarities across different types of pathogens. Using omics, researchers can also better understand human immune responses, including how specific populations would likely respond to a particular vaccine. Figure 1 shows how they were used for COVID-19.

**Figure 1: Researchers used omics and reverse vaccinology to develop COVID-19 vaccines and prioritize vaccine recipients more quickly and effectively.**



Source: GAO analysis and gamelover/fizzaig/stock.adobe.com. | GAO-22-104371

# Next-Generation Vaccine Platforms



Next-generation platforms allow vaccines to be developed based on the pathogen’s genetic information, instead of first growing the pathogen (e.g., a virus) in the lab. As a result, next-generation platforms are highly adaptable, and can potentially accelerate vaccine development.

## What is it?

Next-generation platforms use an interchangeable system of components, allowing vaccines to be developed in a plug-and-play fashion. Next-generation platforms use a carrier to deliver genetic instructions for an antigen—the substance that stimulates an immune response—into the body. Platform based approaches can be scaled up more rapidly, potentially accelerating vaccine development, and can target multiple pathogens (table 1).

**Table 1: Examples of next-generation vaccine platforms**

Vaccine Platform	Description
 <p>DNA</p>	DNA vaccines use synthetic DNA coding for an antigen. The synthetic DNA is inserted into a DNA vector, which delivers it into the body. The body’s cells then convert the DNA to mRNA which, in turn, is converted into the antigen.
 <p>mRNA</p>	Messenger RNA (mRNA) vaccines are encapsulated genetic instructions that allow the body’s cells to directly produce the antigen and stimulate the immune system. Since mRNA is naturally unstable, it is first stabilized and then packaged in a carrier molecule. Lipid nanoparticles—tiny spherical capsules made of lipids—are the most frequently used carriers.
 <p>Viral vector</p>	Viral vector vaccines use other viruses—genetically engineered to remove their disease-causing aspects—as the carrier to deliver the DNA code for an antigen into the body. Viral vector vaccines that reproduce themselves result in more antigen production and thus stimulate a stronger immune response.

Source: GAO analysis. | GAO-22-104371

## How mature is it?

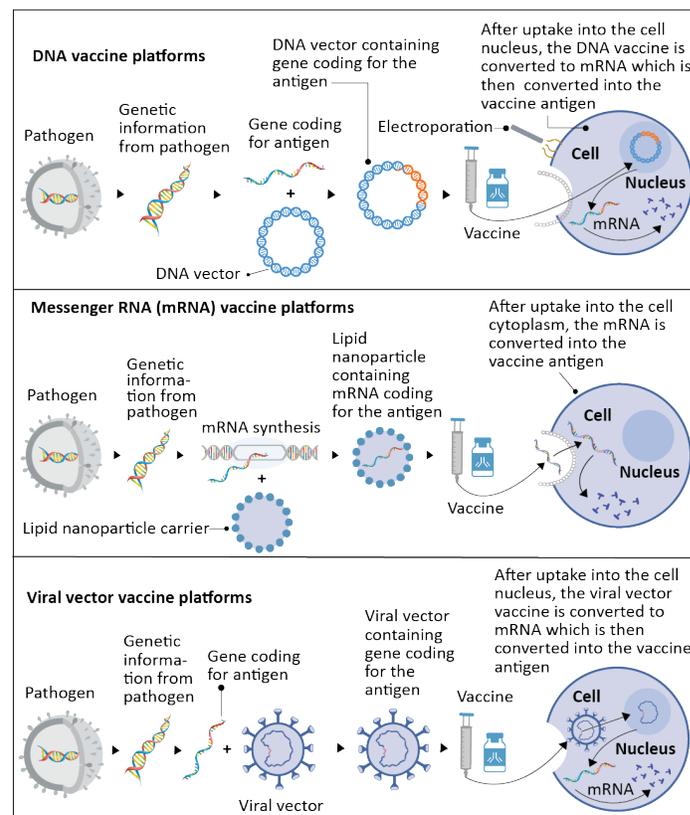
Next-generation vaccine platforms are a recent development. As of October 2021, the Food and Drug Administration (FDA) had licensed two next-generation viral vector platform vaccines for use in humans—one for dengue and one for Ebola, and had issued an emergency use authorization (EUA) for a viral vector COVID-19 vaccine. FDA had also issued EUAs for two mRNA vaccines for COVID-19, and one of these vaccines had also been

licensed for certain individuals. FDA had not licensed any DNA vaccines for use in humans, but had licensed one vaccine for use in animals.

## How does it work?

DNA vaccine platforms contain genetic instructions that induce the cell to make the antigen. The gene encoding the antigen is plugged into a DNA vector to make the vaccine. mRNA vaccine platforms contain synthesized mRNA encoding the vaccine antigen, which is then encapsulated in a lipid capsule to make the vaccine. Viral vector vaccine platforms contain copies of genes encoding the vaccine antigen. The gene is plugged into a viral vector to make the vaccine (fig. 1).

**Figure 1: Vaccine platforms**



Source: GAO (analysis); Adaption of images depicting vaccine technologies with permission from Springer Nature: *Nature* (“The Race for Coronavirus Vaccines: A Graphical Guide,” Ewin Callaway) © 2020 and MariLee/fizzgig/Sir.Vector/stock.adobe.com. | GAO-22-104371

# Nontraditional Methods of Vaccination

Most vaccines are currently administered by injection under the skin or into the muscle. However, injection can be associated with pain and cause anxiety for some individuals. Nontraditional ways of delivering vaccines such as via a nasal spray offer the potential for increased public uptake, better immune responses, and perhaps lower dosages.

## What is it?

Three nontraditional approaches for administering vaccines may address challenges associated with traditional injections. *Dermal* vaccines are delivered by microscopic needle patches through the upper layer of the skin. *Nasal* vaccines are administered via either a mist or drops in the nasal cavity. *Oral* vaccines are delivered in the form of a pill or liquid (table 1).

All three approaches can eliminate the pain and anxiety that some people associate with traditional injections. Other potential benefits include decreasing the requirement for cold storage and reducing the need for trained personnel and injection supplies; these benefits may help increase vaccination rates. Nontraditional approaches can also potentially result in an improved immune response—the production of antibodies and activation of cells to fight a virus or some other microorganism that can cause disease.

**Table 1: Potential opportunities and challenges of nontraditional vaccination methods**

Nontraditional vaccination methods	Potential opportunities	Potential challenges
<b>Dermal</b>	<ul style="list-style-type: none"> <li>• Pain free</li> <li>• Lower dosages</li> <li>• Easy to administer</li> <li>• Does not require cold storage</li> </ul>	<ul style="list-style-type: none"> <li>• Device development for simple, reliable, and reproducible delivery of vaccines.</li> </ul>
<b>Nasal</b>	<ul style="list-style-type: none"> <li>• Pain free</li> <li>• Cost effective</li> <li>• Easy to administer</li> <li>• Fewer supplies</li> </ul>	<ul style="list-style-type: none"> <li>• Vaccine may not remain in the nasal passage long enough for effective absorption.</li> </ul>
<b>Oral delivery</b>	<ul style="list-style-type: none"> <li>• Pain free</li> <li>• Cost effective</li> <li>• Easy to administer</li> <li>• Fewer supplies</li> </ul>	<ul style="list-style-type: none"> <li>• Must be formulated to protect against degradation in the stomach.</li> </ul>

Source: GAO analysis. | GAO-22-104371

## How mature is it?

The Food and Drug Administration (FDA) licensed the first oral vaccine in the 1960s for polio; only a few other oral vaccines have been licensed since then. More recently, dermal and nasal vaccines have been developed for seasonal influenza. Although many traditional (injected) vaccines have been successfully developed and administered over the last century, the number of vaccines available with nontraditional options of

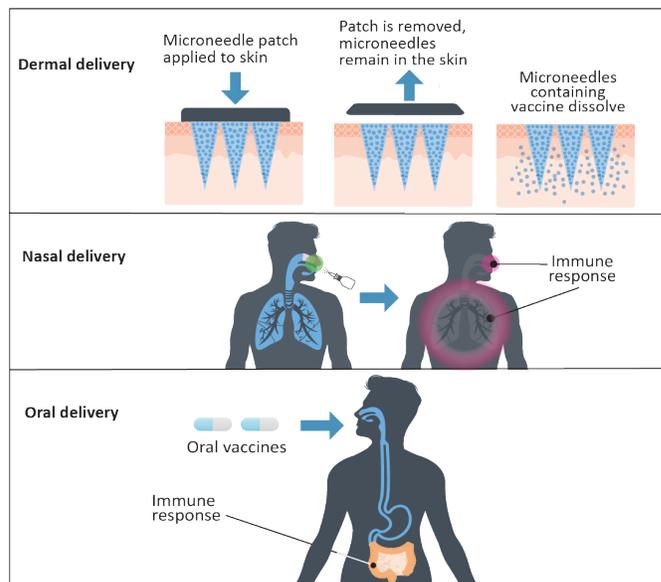
administering remains low. Researchers continue to focus on trying to develop nontraditional routes of vaccination.

## How does it work?

Injected vaccines elicit a systemic immune response in the body's fluids, such as the blood. In contrast, vaccines administered via dermal, nasal, and oral routes produce an immune response in both the blood and in the mucous membranes—the protective lining in areas such as the mouth, nasal passages, and intestines. During this kind of immune response, the cells and antibodies in the mucous membranes block or destroy the invading microorganisms (also known as pathogens). The immune response is helpful in blocking the early stages of infection since most pathogens infect the body through the mucous membranes.

Dermal delivery uses patches covered with hundreds of microscopic needles made from sugar mixed with a vaccine, which dissolve into the skin after penetrating through its upper layer. For nasal delivery, cells in the nasal cavity encounter vaccines, stimulating an immune response in the respiratory tract that blocks a pathogen from entering the body. Oral vaccines are ideally absorbed in the intestines, which contain 70 to 80 percent of all antibody-producing cells in the body (fig. 1).

**Figure 1: Nontraditional vaccination methods**



Source: GAO analysis, Harro© magazine by Harro Hoefliger, Bharat Biotech, and Melazerg/Pavlo Plakhotia/stock.adobe.com. | GAO-22-104371

# Monoclonal antibodies

Monoclonal antibodies are not vaccines. They are laboratory-made proteins that mimic the human immune system's ability to fight off pathogens. These proteins can be developed quickly in response to potential pandemics and used to provide short-term protection against infectious diseases—either as a treatment or as a preventative before someone is infected. They can also be used to complement the human immune system to bolster the protective response in immunocompromised individuals, such as organ transplant recipients.

## What is it?

Monoclonal antibodies are laboratory-produced versions of specific proteins that have been isolated from the antibodies naturally produced by the human immune system to respond to and neutralize invading pathogens. Monoclonal antibodies are emerging as an important approach to preventing infections. A recent study showed that monoclonal antibodies can be effective at preventing malaria, an infectious disease that currently lacks an effective vaccine. An August 2021 study reported that monoclonal antibodies reduced the risk of unvaccinated or immunocompromised people developing any COVID-19 symptoms by 77 percent.

Monoclonal antibodies are different from vaccines in that they do not stimulate long-term protection (table 1).

**Table 1: Monoclonal antibodies and vaccines work differently to protect against disease.**

	Monoclonal antibodies	Vaccines
<b>What is it?</b>	A protein that binds to a pathogen to mitigate effects of an infection	A modified pathogen or a part of a pathogen that triggers the immune system
<b>How is it used?</b>	To provide treatment or short-term protection to avoid infection	To stimulate the immune system to fight against a pathogen
<b>How quickly does it work?</b>	Immediately	Several weeks after all required doses are given
<b>How long does the protection last?</b>	Weeks to months	Years to lifetime (some vaccines require boosters)

Source: GAO analysis. | GAO-22-104371

## How mature is it?

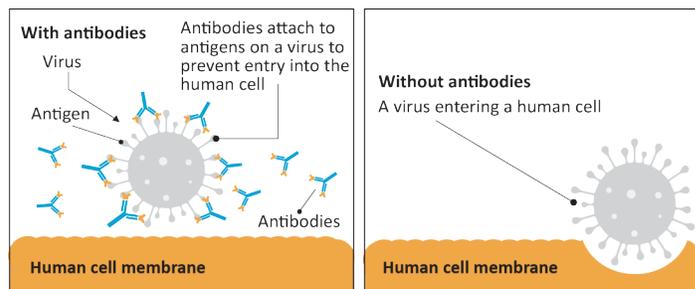
Since their introduction in 1975, monoclonal antibodies have been developed primarily for use as therapeutics against non-

infectious diseases, such as cancer. Of more than 100 monoclonal antibodies licensed by the FDA, only seven are used to prevent or treat infectious diseases. The high cost is a limiting factor, as manufacturing is complex, expensive, and requires specialized personnel.

## How does it work?

Monoclonal antibodies mimic the immune system by binding directly to antigens, the components of a pathogen that stimulate an immune response, preventing them from initiating the infection cycle. During the COVID-19 pandemic, monoclonal antibody products were developed as therapeutics to treat SARS-CoV-2 (the virus that causes COVID-19). As of October 2021, there were four authorized monoclonal antibody treatments for COVID-19. Clinical trial data have also shown that monoclonal antibodies may be effective for pre-exposure prevention of COVID-19, but they have not been authorized or licensed for this use (fig.1).

**Figure 1: Monoclonal antibody targeting SARS-CoV-2, the virus that causes COVID-19**



Source: GAO analysis, and Maryland Department of Health Office of Preparedness and Response, and iierlok\_xolms/stock.adobe.com. | GAO-22-104371

Most monoclonal antibodies have been administered intravenously, but some have been administered by intramuscular or subcutaneous injection. Monoclonal antibodies can target a specific pathogen or be combined into mixtures known as cocktails to target a broad range of variants of the same pathogen. A variant has one or more mutations that differentiate it from other variants of the same pathogen in circulation, and those mutations may protect the virus from being neutralized by an existing monoclonal antibody or vaccine.

Source: ktsdesign/stock.adobe.com (header). | GAO-22-104371

## Appendix III: Testing Technologies and Approaches

We identified six technologies and approaches that may improve vaccine testing. This appendix provides five summaries of these technologies and approaches.

These summaries are based on documents we reviewed and interviews we conducted. Specifically, we reviewed scientific literature describing current and developing tools, interviewed experts from government, academia, the nonprofit sector, and industry, and collaborated with the National Academies of Sciences, Engineering, and Medicine to convene a 3-day expert meeting to discuss these technologies and approaches. Each summary includes information on what the technology or approach is, its maturity, and how it works.

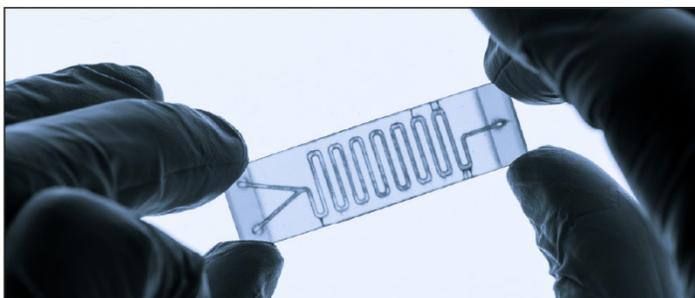
# Organ Chips

Organ chips are small experimental laboratory tools that contain human cells and mimic how organs and systems in the body work. When used individually, they allow researchers to study a particular part of an organ's function. When linked together, they can mimic the interconnectedness of multiple organs in the human body. Organ chips offer a potential alternative to traditional animal testing and could eventually expedite the development and testing of vaccines and drugs, among other things.

## What is it?

Organ chips are designed to reproduce the functioning of human organs or tissues as realistic models. Inside these chips, which are about the size of a computer memory stick, are tiny channels lined with living human cells (fig. 1). Researchers control the external and internal environment around the cells to mimic certain conditions within the human body. For example, they can create movement to mimic breathing motions in the lungs and muscle contractions in the heart. This modeling allows researchers to replicate and study the structural and functional complexity of human organs.

**Figure 1: Example of an organ chip**



Source: luchschenF/stock.adobe.com. | GAO-22-104371

The interaction of multiple organs can be studied by linking two or more organ chips and also by incorporating multiple lines of cells from different organs onto one chip. Using these systems, researchers may be able to gain a deeper understanding of how a vaccine works or how a drug is absorbed, distributed, or metabolized by the body.

## How mature is it?

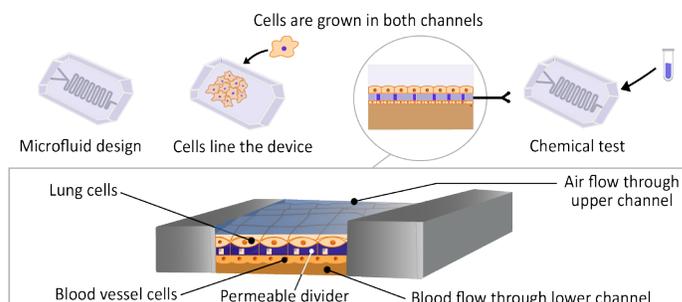
Organ chip technology has been in development for over a decade. Recent advances allow for analyses using integrated multi-chip systems to study complex interactions among multiple organs and tissues, including liver, lungs, heart, intestines, bone marrow, kidneys, and lymph nodes. However, further advances in design may be needed to investigate some types of organ and cell functions. For example, more complex designs may be needed for chips containing multiple types of cells that differ from one another in the amount of time they need to grow and their responses to various stimuli.

## How does it work?

Organ chips contain tiny channels that mimic the flow of substances like blood and air through tissues and organs, similar to what occurs in the human body. For example, a lung organ chip may have a main channel that is divided in half lengthwise to create a top and bottom. In the upper section, lung cells interact with air that flows through the channel. In the lower section, blood vessel cells interact with the flow of a liquid medium that imitates blood. Crucially, the divider between these sections is permeable, allowing the exchange of molecules between the different types of cells. Researchers can then study the effects of bacterial or viral infections by introducing the pathogen to the air flow channel. They can also test drugs by administering the drug into the blood in the lower channel (fig. 2).

Using organ chip technology in this way, researchers might be able to study how SARS-CoV-2 infects the lungs when a patient contracts COVID-19 without relying on animal studies, which may not reliably predict human responses.

**Figure 2: A chip containing lung cells and blood vessel cells can be used to study the effects of pathogens or drugs in the human lungs.**

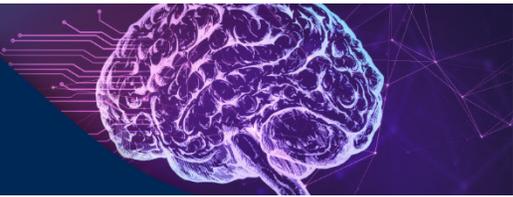


Source: GAO analysis, Wyss Institute at Harvard University, and J.E. Sosa-Hernández et al., "Organs-on-a-Chip Module: A Review from the Development and Applications Perspective," *Micromachines*, vol. 9, no. 10 (2018): 536. License: CC BY 4.0. <https://creativecommons.org/licenses/by/4.0/legalcode>. | GAO-22-104371

Similarly, different types of organ chips could be used to understand other pathogens or to study the effects of vaccines. For example, in one study, researchers administered a flu vaccine to lymph node chips to observe patient-specific antibody responses, which demonstrated the chip's potential as a preclinical tool to study human responses to vaccines.

Source: luchschenF/stock.adobe.com (header). | GAO-22-104371

# Artificial Intelligence and Machine Learning



Artificial intelligence and machine learning (AI/ML) techniques use computer systems and algorithms to produce data-driven insights that allow vaccine developers to make discoveries during research and development (R&D) and clinical testing. Some of these insights may allow for more efficient clinical trials and generate predictions that could result in safer, more effective vaccines in less time.

## What is it?

AI/ML is a set of advanced technologies that can perform complex tasks and analyze vast amounts of data to develop new insights, including for designing vaccines (table 1). Early AI technologies often used computer programs to make rules-based decisions. Later, the incorporation of mathematics and probability led to ML, which uses a variety of data analytics approaches to improve prediction.

**Table 1: AI/ML techniques used in vaccine development**

AI/ML techniques	Description
 Artificial intelligence	Artificial Intelligence (AI) refers to the capacity of computers or other machines to exhibit or simulate intelligent behavior. AI-based approaches have been used in vaccine design to predict potential epitopes—the part of an antigen to which an antibody binds.
 Machine learning	Machine Learning (ML) is a family of statistical and mathematical modeling techniques that use data to train an algorithm or system to perform tasks. ML has been used to identify antigens from protein sequences.
 Deep learning	Deep Learning is a class of ML that processes input data to provide outputs that can be used to extract findings. Deep learning has been used to simulate coronavirus spike proteins and identify possible targets for vaccine design.

Source: GAO analysis of literature; kornkun/stock.adobe.com. | GAO-22-104371

## How mature is it?

AI/ML techniques have advanced to the point where they are being used throughout vaccine development. However, the use of AI/ML in clinical trials is less mature due to limitations on access to patient data and other issues. Also, techniques like deep learning require large quantities of data which may not be available during a clinical trial.

## How does it work?

In the early stages of vaccine development, researchers use AI/ML techniques to mine biological data to screen and identify

antigens for potential use in vaccines. Deep learning methods can help researchers identify antibodies for their potential to bind to a given antigen, which may accelerate and improve the development of a new vaccine.

During clinical trials, researchers can use AI/ML to identify suitable participants, optimize design variables, and predict responses (fig. 1). For example, using data sources such as electronic health records (EHR) and genomics data, researchers may determine who is suitable based on trial criteria. They can then identify the optimal number of patients needed for the trial. Once data collection begins, researchers can analyze the data coming in, which may help identify subgroups likely to respond differently to various vaccines or dosages, among other things.

**Figure 1: Artificial intelligence (AI) and machine learning (ML) can use various types of data to enhance vaccine development**



ML can use health record data to efficiently identify and select patients for trials.



ML can use data from wearable devices to detect relevant events in real time.



ML can use omics data to identify sets of genes that predict the ability of a vaccine to induce an immune response.



ML can use imaging data to analyze virus structures to more quickly design vaccines that will prevent infection.

Source: GAO analysis and Dragonimages/ballball14/arcyto/Jezper/stock.adobe.com. | GAO-22-104371

AI/ML techniques can also help vaccine developers predict the immune response a vaccine may induce. Using these techniques to analyze omics data from the blood of trial participants who have received the vaccine may allow researchers to predict whether someone will have a high or low antibody response and the likelihood of experiencing an adverse event. This approach has been used in vaccines developed against yellow fever, influenza, and malaria, and may improve the ability to estimate vaccine effectiveness.

# Electronic Health Records



An electronic health record (EHR) is a digital record of a patient's medical information. EHRs could be used in clinical trials to streamline patient recruitment and data collection, and improve data accuracy. EHRs can facilitate post-trial follow-up of large numbers of patients, which can help researchers better understand how long a vaccine's immunity lasts. EHRs also provide a data source that can be used to generate real-world evidence included in prospective clinical investigations.

## What is it?

EHRs store patients' health data, which include both structured data (e.g., diagnosis codes and lab results) and unstructured narrative data (e.g., clinical notes about symptoms and pathology reports). Because EHRs are used primarily in direct patient care, they are typically used and maintained by health care providers. EHR systems may also allow clinical researchers to access, combine, aggregate, and analyze many types of data for research purposes (table 1), including vaccine studies.

**Table 1: Examples of data typically stored and not stored in electronic health records (EHR)**

Examples of structured data stored in EHRs	Examples of narrative data stored in EHRs	Data unlikely to be stored in EHRs
<ul style="list-style-type: none"> <li>• Date of birth</li> <li>• Sex</li> <li>• Vital signs</li> <li>• Most lab test results</li> <li>• Medications prescribed</li> <li>• Diagnosis (coded)</li> </ul>	<ul style="list-style-type: none"> <li>• Symptoms of illness</li> <li>• Family history of illness</li> <li>• Meaning of physical exam findings</li> <li>• Some lab test results</li> <li>• Pathology reports</li> <li>• Diagnosis (descriptive)</li> </ul>	<ul style="list-style-type: none"> <li>• Place of birth</li> <li>• Gender identity</li> <li>• Survivorship care planning</li> <li>• Living conditions</li> <li>• Psychological distress</li> <li>• Patient-reported outcomes</li> </ul>

Source: E. Kim et al., "The Evolving Use of Electronic Health Records (EHR) for Research," *Seminars in Radiation Oncology*, vol. 29, no. 4 (2019): pp.354-361. | GAO-22-104371

## How mature is it?

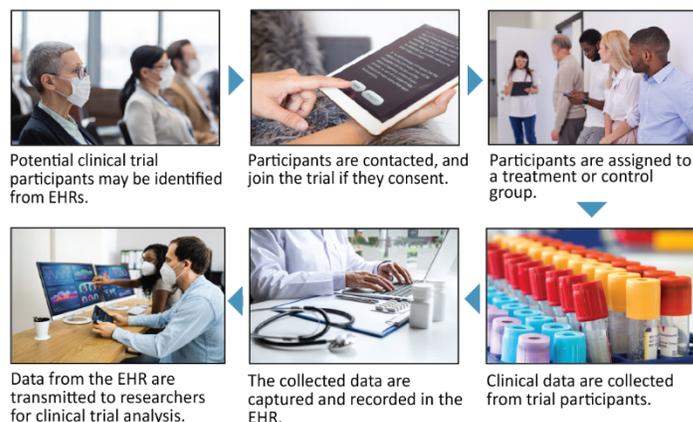
EHRs have been widely adopted in clinical care, but are not in widespread use for clinical trials. Standardized data formats are being developed, and new Department of Health and Human Services rules are addressing interoperability issues. The rules should help address that some EHR systems are not interoperable with electronic data capture systems that manage clinical trial data. As a result, researchers have not always been able to easily transmit data from EHRs for analysis. Interoperable systems allow clinical care staff to enter data into patient records during the patient's visit and the patient's data—such as demographics, vital signs, and medications—automatically populate forms or other records.

Source: metamorworks/stock.adobe.com (header). | GAO-22-104371

## How does it work?

EHRs could be used throughout the clinical trial process, subject to privacy protections. At the beginning, they can reduce the need for paper-based recruitment and manual entry of participant data. Researchers can search databases to identify people who meet the criteria to participate, then study coordinators can contact individuals to obtain consent to enroll them in the trial and use their EHR data. Participants could then be assigned to either an experimental group that receives the vaccine or a control group that receives a placebo. As the clinical trial proceeds, researchers can capture and analyze data from EHRs—potentially during a patient's visit to a clinic—which may provide access to many types of data for review that can supplement the data collected for clinical trials and facilitate post-trial follow-up to assess safety and effectiveness (fig. 1).

**Figure 1: Streamlining the clinical trial process with electronic health records (EHR)**



Source: GAO analysis and luchschenF/Roman/Vinnstock/Popov/LightfieldStudios/Thitiphat/stock.adobe.com. | GAO-22-104371

EHRs are also used to monitor vaccine safety once a vaccine has been licensed and is given to patients. FDA's Biologics Effectiveness and Safety system monitors data in EHRs and other sources to detect adverse events and study specific safety questions for vaccines including for sub-populations such as individuals who are pregnant or have pre-existing conditions.

# Standardized Assays and Common Control Groups

Using standardized assays and common control groups together can help vaccine developers better identify effective vaccine candidates. With this approach, multiple vaccine developers use the same assays (tests that measure a vaccine’s immunogenicity, or ability to induce an immune response) to test multiple vaccine candidates and share a single control group during the clinical trials for those vaccines.

## What is it?

Standardized assays are tests that vaccine developers may use in evaluating candidates, allowing them to measure immune responses the same way (table 1).

**Table 1: Selected assays used in vaccine development**

Purpose	Assay description
<b>Humoral antibody response</b>	Measurement of total or functional antibody levels in the blood
<b>Cell-mediated immune response</b>	Measurement of immune cell responses upon exposure to specific antigens

Source: GAO analysis and M. Dotzert, “Assay Development: Vaccines,” *Lab Manager*, vol. 14, no. 5 (June 2019): pp.40-43. | GAO-22-104371

A common control group may be a single group of placebo-receiving clinical trial participants that is shared by multiple vaccine developers. Members of a common control group do not receive a vaccine. They generate clinical trial data that are compared to data from participants in other groups who may receive different vaccines or different versions or dosages (amounts) of the same vaccine. This approach eliminates the need for each developer to recruit its own control group, reducing the total number of participants needed. In addition, participants outside the control group have a greater chance of receiving a vaccine candidate than a placebo, which may increase clinical trial participation.

## How mature is it?

Standardized assays have been used in vaccine trials, including phase 3 clinical trials of COVID-19 vaccines, according to The National Institutes of Health. Assays may require modifications during the vaccine development process, which is a challenge to standardization. However, some international organizations are collaborating to develop standardized assays for use against known pathogens in advance of potential future outbreaks to enable faster development of vaccines.

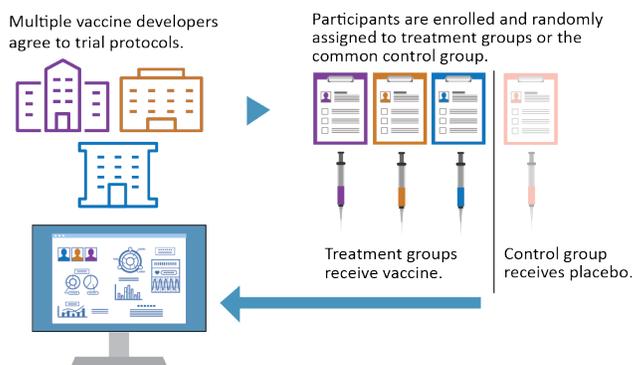
Common control group trials were first used over 20 years ago to accelerate the process of drug development. Since then, they have been used mostly in phase 2 and phase 3 clinical trials of different drugs and drug dosages. However, it may be difficult to use common control groups in clinical trials of multiple vaccine candidates in part due to logistical challenges of coordinating among multiple developers in a single trial.

## How does it work?

To develop a standardized assay, researchers generally begin by obtaining blood samples from patients who have contracted a disease. This information helps vaccine developers understand how a patient’s immune system responds to the pathogen and builds immunity. Developers can then find ways to measure immune responses, such as developing tests to detect pathogen-specific antibodies. They evaluate these assays for precision and may refine them based on performance criteria as vaccines are being developed. Researchers then write standard protocols defining the methodology to allow the assay to be used in the same way by other vaccine developers. This may involve preparing biological reference standards—rigorously evaluated samples used to determine whether an assay is functioning correctly—which can help ensure that data produced in different laboratories are comparable.

Once developers have completed all preclinical testing requirements and agreed to the common control group design, enrollment of participants begins. Each person is assigned randomly to either a group in which they receive one of the vaccine candidates or a common control group that receives a placebo (fig. 1).

**Figure 1: Example of a possible trial design using standardized assays and common control groups**



The same assays are used with all vaccines to measure and compare immune response.

Source: GAO analysis and Kornkun/pp7/stock.adobe.com. | GAO-22-104371

Combining standardized assays with common control groups allows for apples-to-apples comparisons of the vaccine candidates. Investigating multiple vaccines at once could help identify the most effective vaccines against a disease and provide more rapid and reliable results.

# Virtual Clinical Trials and Wearable Devices



Virtual clinical trials, also referred to as decentralized trials, and wearable devices, also referred to as digital health technologies, work together to capture health data remotely, potentially eliminating the need to travel to a clinic or office to participate in a clinical trial. This approach makes it easier for more people to participate, thereby broadening the pool of potential candidates. Virtual clinical trials may also streamline data collection and reduce errors by eliminating the need for staff to collect and record data.

## What is it?

Virtual clinical trials may use web-connected devices to extend the reach of clinical investigations to where participants live and work without compromising study design (table 1). Once clinical trial participants are connected electronically, they can submit their data via wearable devices as well as mobile phones and tablets. Researchers then use the data to assess outcomes and observe physical activity remotely. This approach has been used, for example, to test new medicines and assess the effect of behavioral interventions to treat depression.

**Table 1: Comparison of traditional and virtual clinical trials**

Clinical trial element	Traditional clinical trial	Virtual clinical trial
Study design	May use a randomized control trial design	May use a randomized control trial design
Health monitoring	On-site	Remote
Patient reported data	Submitted periodically during clinic visits	Submitted more frequently via devices

Source: GAO analysis. | GAO-22-104371

Wearable devices can look similar to commercially available fitness trackers and sometimes use clothing-embedded sensors to collect health data continuously as people go through their daily routines. Many wearable devices measure heart rate and blood pressure, allowing for monitoring of cardiac events. Wearables have also been developed to measure sleep and movement disorders, monitor glucose levels, and measure tremors experienced by patients with Parkinson’s disease.

## How mature is it?

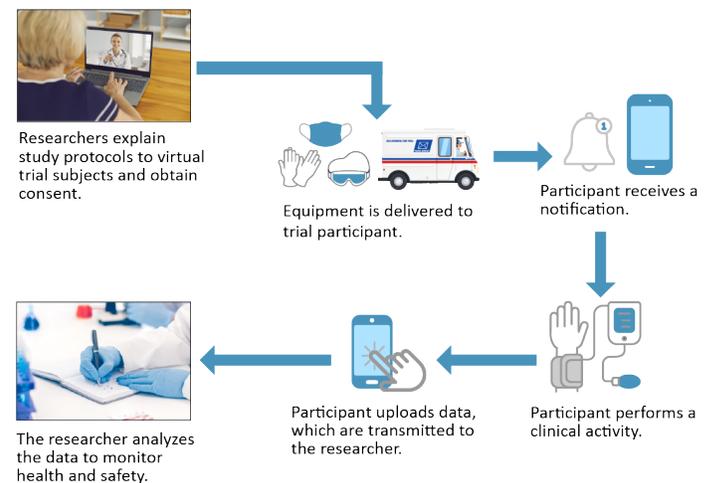
The first virtual clinical trial began in 2011 but experienced technical challenges and was not completed. Since then, companies are increasingly leveraging digital capabilities to conduct virtual trials. These advances allowed some planned traditional trials to be conducted virtually during the COVID-19 pandemic. For example, researchers used some elements of virtual trials—such as remote screening to determine patients’ risk status and remote reporting of symptoms and study data—in clinical trials to test vaccines against COVID-19.

## How does it work?

While traditional clinical trials require a physical, centralized site where patients report for in-person visits, a

virtual trial begins with online recruiting followed by informed consent and participant enrollment, also handled electronically. If a vaccine is designed to be self-administered (e.g., dermal, nasal, or oral delivery) and does not require special storage, it could potentially be sent to participants’ homes in a fully virtual trial. However, vaccine trials would likely retain some features of traditional trials such as in-person vaccination. Study staff may also prompt participants via apps and text messaging for adherence to other study protocols (e.g., reporting symptoms) and conduct clinical evaluations via telemedicine. Participants can perform some clinical procedures such as using a finger stick device to obtain a drop of blood for analysis, results of which may be mailed back to researchers. When wearable devices are used, the data would be collected and transmitted to researchers via a smartphone app or web-based interface (fig. 1).

**Figure 1: Possible data collection process for virtual trials**



Source: GAO analysis and StudioRomantic/sla009/Agus/SirVector/yurolaitsalbert/Barkwoodsdesign/AAVAA/stock.adobe.com. | GAO-22-104371

Researchers might assess outcomes of virtual clinical trials by conducting interviews remotely and tracking participants’ electronic health records (EHR). For example, researchers can connect telemedicine equipment such as blood glucose-monitoring devices via wireless data transmission to EHR systems. This allows clinical data to be sent directly to patient records, enabling real-time data collection of more data for faster clinical trials and more robust analysis.

## **Appendix IV: Manufacturing Technologies and Approaches**

We identified five technologies and approaches, collectively known as bioprocess intensification that may improve vaccine manufacturing. This appendix provides a summary of these technologies and approaches.

This summary is based on documents we reviewed and interviews we conducted. Specifically, we reviewed scientific literature describing current and developing tools, interviewed experts from government, academia, the nonprofit sector, and the research industry, and collaborated with the National Academies of Sciences, Engineering, and Medicine to convene a 3-day expert meeting to discuss these technologies and approaches. Each summary includes information on what the technology or approach is, its maturity, and how it works.

# Bioprocess Intensification



Bioprocess intensification can improve vaccine manufacturing flexibility and productivity through flexible facilities, more productive equipment, and improved technologies. To improve flexibility, vaccine manufacturers can use modular bioprocessing systems, single-use systems, and cell-free synthesis that provide the ability to rapidly switch between vaccines, scale up production, or relocate production capacity. To improve vaccine manufacturing productivity, manufacturers can use process optimization technologies to, for example, improve the cells and growth ingredients used to produce vaccine antigens and automated, continuous processing systems that run with fewer interruptions.

## What is it?

Bioprocess intensification combines flexible facilities, more productive equipment, and improved technologies to enhance vaccine manufacturing flexibility and productivity while reducing costs and time. Modular bioprocessing systems have flexible infrastructure components, similar to building blocks, that may replace the fixed rooms and areas dedicated to specific bioprocessing steps and provide the ability to rapidly switch between vaccines, scale up production, or relocate manufacturing capacity. Single-use systems are equipment and materials composed primarily of disposable, sealed, pre-sterilized plastic components designed to be used once. Continuous processing systems consist of automated equipment that seamlessly integrates all vaccine production and processing steps, including filling and packaging—also known as fill-finish. Process optimization includes, but is not limited to, improving the cells and cell growth ingredients used to produce vaccine antigens—the component of the vaccine that stimulates the immune systems. Cell-free synthesis uses biological molecules in place of living cells to make the vaccine antigens (fig.1).

**Figure 1: The three parts of bioprocess intensification**



Source: GAO. | GAO-22-104371

## How mature is it?

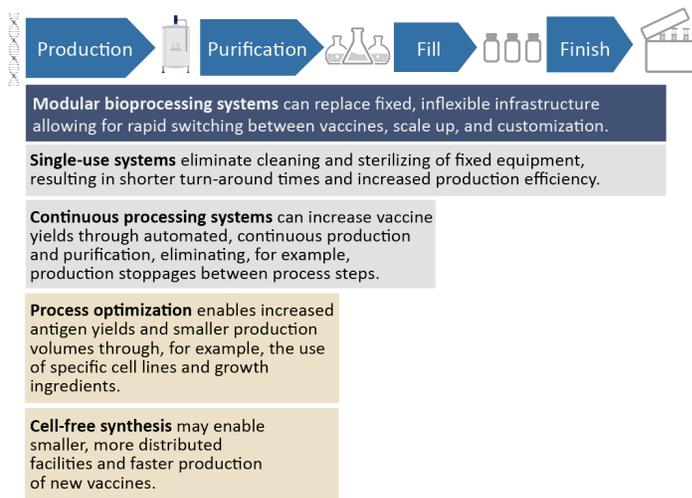
For decades, other industries, such as chemical manufacturing, have used flexible facilities, more productive equipment, and improved technologies similar to those used in bioprocess intensification. Over the past 20 to 30 years, these three categories have been used for pharmaceutical applications, including vaccine manufacturing. For example, single-use systems began to emerge in the early 1980s and continue to be adopted over traditional fixed systems. Further, in the last two decades, cell-free synthesis has surged to meet the increased production demand of inexpensive proteins and small molecules, most recently for generating the mRNA used in the COVID-19 mRNA vaccines.

Source: whyframeshot/stock.adobe.com (header). | GAO-22-104371

## How does it work?

Bioprocess intensification can be applied at different points in the vaccine manufacturing process. Modular bioprocessing systems work by breaking manufacturing components into smaller functional blocks, such as prefabricated rooms, which may be added into existing facilities to increase flexibility. These systems typically include single-use systems that replace fixed equipment and materials with disposable equipment and materials that are discarded after each use. This eliminates the need for cleaning and sterilization required for fixed equipment. Continuous processing systems integrate and automate all manufacturing steps with few or no interruptions, unlike traditional processes that stop after certain steps, such as cell growth. Process optimization uses approaches to improve the efficiency and productivity in each step of manufacturing. For example, improving cell growth characteristics and growth ingredients used in antigen production can greatly increase yields without adding capacity. Cell-free synthesis combines purified biological molecules in reactor vessels to synthesize antigens, which are then formulated into vaccines. This eliminates the need to grow large amounts of living cells to produce the antigen used in the vaccine (fig.2).

**Figure 2: Bioprocess intensification**



Source: GAO analysis of scientific literature and rashadashurov/tutti\_frutti/StockBURIN/divstock/stock.adobe.com. | GAO-22-104371

## Appendix V: Expert Participation

We collaborated with the National Academies of Sciences, Engineering, and Medicine to convene a 3-day meeting of experts to inform our work on vaccine development; the meeting was held virtually on January 25-28, 2021. The experts who participated in this meeting are listed below. Many of these experts gave us additional assistance throughout our work, including ten experts who provided additional assistance during our study by sending material for our review or participating in interviews; and 9 experts who reviewed our draft report for accuracy and provided technical comments.

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Bioprocess Advantage LLC

**Ruth A. Karron, MD**

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Founding Director  
Johns Hopkins Vaccine Initiative

**Jason Kelly, PhD**

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**Jerome Kim, MD**

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**Christopher Snyder, PhD**

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### Staff acknowledgments

In addition to the contact named above, Sarah Harvey (Assistant Director), Robert Rivas (Analyst-in-Charge), Nora Adkins, Cheron Brooks, Virginia Chanley, Mike Dickens, Kaitlin Farquharson, Louise Fickel, Cory Gerlach, Cindy Korir-Morrison, Anika McMillon, Silda Nikaj, Monica Perez-Nelson, and Michael Walton made key contributions to this report. Sean Amberger, Patricia Edouard, and Eric Lee also contributed to this report.

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