GAO

United States Government Accountability Office

Report to Congressional Committees

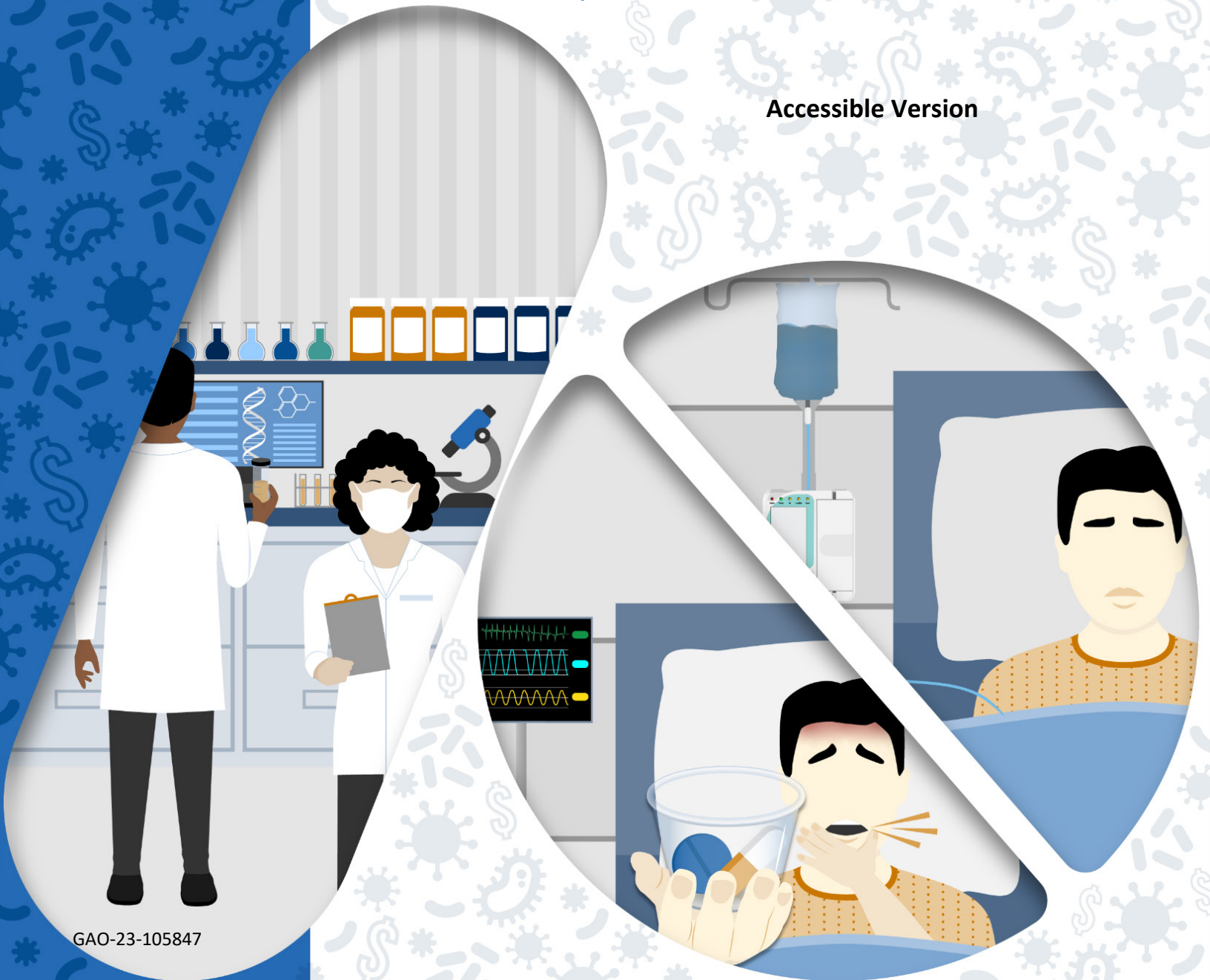
September 2023

TECHNOLOGY ASSESSMENT

# Antiviral Drugs

## Economic Incentives and Strategies for Pandemic Preparedness

**Accessible Version**



GAO-23-105847

The cover image displays a stylized representation of antiviral drug research and development in a scientific lab and an individual receiving an antiviral drug intravenously and in pill form.

Cover source: GAO. | GAO-23-105847

Highlights of GAO-23-105847, a report to congressional committees

September 2023

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# Antiviral Drugs

## Economic Incentives and Strategies for Pandemic Preparedness

### Why GAO did this study

Pandemics impose large human and economic costs on society. According to the World Health Organization, almost 7 million people died worldwide during the COVID-19 pandemic. The International Monetary Fund estimates that by 2024, COVID-19 will have reduced global economic output by $13.8 trillion relative to prepandemic forecasts. Scientists have predicted that another pandemic is highly likely.

The CARES Act included a provision for GAO to report on the federal response to the COVID-19 pandemic. This report discusses incentives and strategies to enhance antiviral drug investment.

GAO reviewed economic and scientific literature relevant to these areas. GAO also interviewed stakeholders and experts with perspectives on the science and economics of antiviral drug development, including those at HHS. In addition, GAO convened, with assistance from the National Academies of Sciences, Engineering, and Medicine, a 2-day meeting of 16 experts.

GAO is identifying policy options in this report.

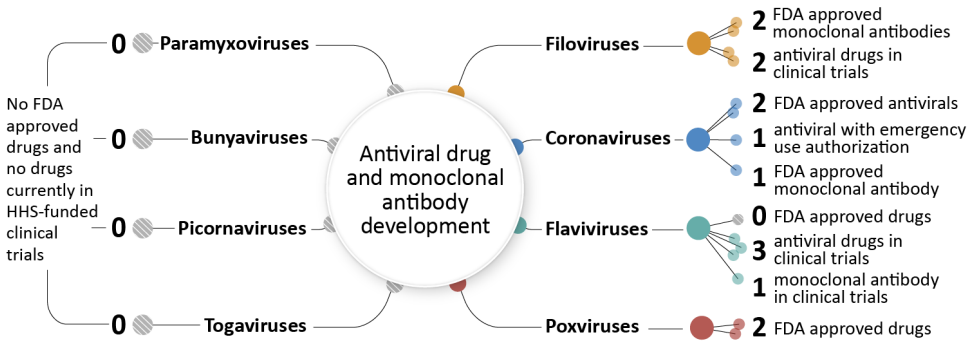
View GAO-23-105847. For more information, contact Michael Hoffman at (202) 512-2700, HoffmanME@gao.gov or Candice Wright at (202) 512-6888, WrightC@gao.gov.

### What GAO found

Antiviral drugs help the body fight off harmful viruses and can ease symptoms and shorten the length of an infection. Some of these drugs can be broadly acting—that is, they can treat infections from multiple viruses. This makes them especially valuable in a future pandemic where the viral threat is unknown in advance. Some scientists predict that viruses are most likely to be the source of the next pandemic because they are able to spread rapidly and because there are fewer treatment options for viruses.

The National Institutes of Health (NIH) has identified several viral families that have potential to cause future pandemics. However, as of May 2023, no known drugs for a number of these viral families had been approved or were in clinical trials funded by the Department of Health and Human Services (HHS), according to HHS. GAO identified a number of technologies to speed antiviral drug development, such as using artificial intelligence to identify drug candidates.

**State of Drug Development for Viral Families with High Potential to Cause Future Pandemics**




FDA = U.S. Food and Drug Administration
HHS = Department of Health and Human Services

Source: GAO analysis of HHS and other documentation; GAO (icons). | GAO-23-105847

Note: Monoclonal antibodies are lab-produced proteins that can be used to treat or prevent viral infections. Graphic refers to clinical trials funded by either the Biomedical Advanced Research Development Authority or the National Institute of Allergy and Infectious Disease within the Department of Health and Human Services (HHS).

Experts GAO spoke with noted that a number of factors complicating the market's efficient functioning make it unlikely that market forces alone will induce the development of antiviral drugs at levels that would maximally benefit society and aid future pandemic preparedness. However, policymakers could use several mechanisms to incentivize investment in antiviral drugs. "Push" mechanisms, such as research grants, can incentivize early research, while "pull" mechanisms, such as purchase commitments, can incentivize the production of completed antivirals.

In 2022, the White House issued the *National Biodefense Strategy and Implementation Plan*, which called for the development of two novel antiviral drugs. Experts GAO spoke with also identifed a number of approaches to guide the use of economic incentives. These approaches include developing (1) a number of antiviral drugs to the point of phase 1 clinical trials, which could be less costly than developing fully approved drugs; (2) a wide range of antiviral drugs that act against different parts of the viral lifecycle; and (3) broadly acting antiviral drugs for a wide range of pathogens.

GAO identified three policy options that may help to spur antiviral drug development. These policy options are provided to inform policymakers—including Congress, federal agencies, state and local governments, academia, industry, and international organizations—about potential approaches and actions to address gaps highlighted in this technology assessment. Policymakers would need to consider how to align these potential actions with existing federal programs and initiatives. See below for a summary of policy options as well as related opportunities and considerations.

**Policy Options to Facilitate the Development of Antiviral Drugs for Future Pandemics**

| Policy option | Opportunities | Considerations |
|---|---|---|
| **Create a strategy to focus on developing diverse antiviral drugs to respond to pandemics caused by the most dangerous pathogens** (report p. 33).<br><br>Policymakers could ensure focus on pathogens and pathogen families, such as flaviviruses and bunyaviruses, that are most likely to cause severe future pandemics, with an emphasis on pathogen families for which no drug candidates are currently in clinical trials. | • Designing hypothetical pandemic scenarios could help identify the relative likelihoods that an outbreak could quickly become severe and widespread, indicating which antiviral drugs may need to be stockpiled and which need to be developed only to the point of phase 1 clinical trials.<br>• Focusing attention on viral families with no drug candidates in clinical trials could spur research and development.<br>• Developing drug candidates through phase 1 clinical trials would provide information on the initial safety profile and side effects of different doses in advance of potential pandemics. | • Not every possible pandemic scenario can be considered, and a pathogen that may cause a future pandemic might not appear on current lists of potential pandemic pathogens.<br>• It is difficult to predict how a novel pathogen may travel across populations. Therefore, assessing the stage to which each drug candidate should be developed and how much manufacturing might be needed may also be difficult. |
| **Assign to a new or existing entity the authority to lead, implement, and be accountable for identifying and developing antiviral drugs for pathogens or pathogen families of greatest risk** (report p. 34).<br><br>Policymakers could ensure that this entity has authority and accountability for making decisions and allocating resources to implement a strategy for addressing pathogens and pathogen families informed by pandemic scenarios and the risks they present. | • A single, centralized entity could direct strategic investments for pandemics, increase communication across federal agencies and with drug developers, and facilitate greater accountability for more effective allocation of resources and response to the spectrum of pandemic threats.<br>• A single entity that is explicitly accountable for pandemic preparedness and response could effectively mitigate pandemic risks and enhance government efforts to deal with uncertain but likely pandemic risks. When multiple entities share fragmented responsibilities, no one entity is accountable for the ultimate success of the effort. | • Because authorities among HHS entities vary, designating an entity with responsibility and authority may require new directives or legislation.<br>• To be effective, any entity with such authority for identifying and developing pandemic antiviral drugs would need to coordinate or align its efforts with related efforts, such as the development of vaccines, diagnostics, and surveillance. |
| **Implement economic incentives to develop antiviral drug candidates and spur new drug-development technologies** (report p. 35).<br><br>Policymakers could use various push and pull economic incentives to encourage the development of pandemic antiviral drugs, based on the economic costs of scenarios, scientific opportunities, and pathogen priorities. They could also consider other policy priorities, such as drug accessibility.<br><br>Policymakers could use economic incentives to stockpile certain drugs in advance as well to ensure sufficient manufacturing capacity. | • Economic incentives could address the identified challenges related to critical market failures that have limited investment in pandemic antiviral drugs. Through such actions, economic and societal costs from viral pandemics could be meaningfully reduced.<br>• Manufacturing capacity for pandemic antiviral drugs may be useable for similar antiviral drugs with an existing commercial market.<br>• New drug development technologies spurred by investment in pandemic antiviral drugs may allow for the treatment of nonpandemic infectious diseases, especially diseases caused by pathogens in the same family as those targeted for antiviral development. | • Periodic updates to evaluations of pandemic risks would be needed to guide the deployment of economic incentives for new antivirals and drug development technologies and the extent of investment needed as new pandemic pathogens arise.<br>• Evidence of the full range of potential pandemic costs may be unavailable or insufficient for precise determinations of the level of investment needed to achieve certain levels of preparedness. |

Source: GAO. | GAO-23-105847

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## Figures

# Abbreviations

| | |
|---|---|
| AI | artificial intelligence |
| APP | Antiviral Program for Pandemics |
| ASPR | Administration for Strategic Preparedness and Response |
| BARDA | Biomedical Advanced Research and Development Authority |
| CARES Act | The Coronavirus Aid, Relief, and Economic Security Act |
| CDC | Centers for Disease Control and Prevention |
| COVID-19 | coronavirus disease 2019 |
| FDA | Food and Drug Administration |
| HHS | Department of Health and Human Services |
| ML | machine learning |
| NCATS | National Center for Advancing Translational Sciences |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| WHO | World Health Organization |

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Scientists have predicted that another pandemic is highly likely.[1] These events can be devastating in terms of loss of life and economic hardship. Broad-spectrum antiviral drugs, which can treat a range of viral infections, can play an important role in pandemic preparedness and response if they are effective against a newly emerged pathogen.

With the COVID-19 pandemic, the world has seen the clinical use of antiviral drugs on an unprecedented scale. During the pandemic, U.S. policymakers—including Congress, federal agencies, academics, industry, and U.S.-based international organizations—focused on developing and scaling up the supply of vaccines and therapeutics. The private sector, in collaboration with the federal government, developed several COVID-19 vaccines at record speeds.

Broad-spectrum antiviral drugs could theoretically be available for the treatment of infected patients at a pandemic's onset—unlike vaccines, which may not be available during the early stages of a pandemic.[2] However, we have previously found that some pandemic preparedness efforts can be limited by uncertainties about market size and financial returns on treatments for pandemic pathogens that have not emerged, reducing incentives for developing these drugs.[3]

For any of the following reasons, therapeutic antiviral drugs may play a vital role in planning for and responding to future pandemics:

- They are designed to treat patients diagnosed with diseases, such as COVID-19, whereas vaccines are meant to protect healthy individuals.
- Millions of individuals could become infected while a vaccine is being developed.

[1]Scientists have estimated that the probability of observing pandemics similar to the COVID-19 pandemic in one's lifetime is about 38 percent and that this probability may double in the coming decades. See Marco Marani et al., "Intensity and Frequency of Extreme Novel Epidemics," *Proceedings of the National Academy of Sciences*, vol. 118, no. 35 (2021).

[2]This report focuses on pandemic threats posed by viral pathogens and antiviral drug research and development that could address these threats. Future pandemics may be caused by either viral or bacterial pathogens and researchers have expressed concerns about certain fungal species that represent threats to public health. We have previously reported on federal actions to address antibiotic resistant bacterial pathogens that may cause future pandemics. See GAO, *Antibiotic Resistance: Additional Federal Actions Needed to Better Determine Magnitude and Reduce Impact*, GAO-20-341 (Washington, D.C.: Mar. 30, 2020).

[3]See GAO, *Vaccine Development: Capabilities and Challenges for Addressing Infectious Diseases*, GAO-22-104371 (Washington, D.C.: Nov. 16, 2021).

- Some pathogens are difficult to vaccinate against.[4]
- Some vaccines demonstrate limited effectiveness.
- Some vaccines are not suitable for certain populations.[5]
- Some individuals may be unwilling or reluctant to be vaccinated because they are concerned about vaccine safety or believe that infection is not a serious threat.

To help guide U.S. efforts on pandemic preparedness, including developing antiviral drugs to prepare for future pandemics, in October 2022, the White House released the updated *National Biodefense Strategy and Implementation Plan*.[6] The strategy calls for establishing a domestic therapeutic research, development, manufacturing, and delivery capability that will yield a range of safe and effective therapeutics that can be available before, or readily created during, a national or international significant biological incident. [7] The strategy also calls for establishing a domestic capability that can identify, develop, test, authorize, manufacture, and deploy new and repurposed therapeutics that meet certain criteria. Further, the strategy calls for developing and achieving Food and Drug Administration (FDA) approval for at least two novel antiviral drugs that meet certain criteria, while targeting outbreak prone viral families that will be ready for domestic stockpiling within 5 years.

The CARES Act includes a provision for GAO to report on the federal response to the COVID-19 pandemic.[8] This technology assessment is part of our body of work in response to the CARES Act. It is also related to the Department of Health and Human Services' (HHS) leadership and coordination of public health emergencies, which we identified as an area of high risk due

[4]The characteristics of some viral pathogens can make vaccine development difficult. For example, there is currently no vaccine to prevent HIV or the hepatitis C virus (HCV). This is because, among other reasons, HIV integrates itself into host cell DNA, limiting the use of vaccines to prevent it. Similarly, HCV has many strains, called genotypes, and many subtypes. To be effective, a vaccine must be able to protect against all or most of a targeted virus's genotypes and subtypes. See Morgan Coulson, *Why Don't We Have an HIV Vaccine?* (Baltimore, Md.: Johns Hopkins Bloomberg School of Public Health, 2022), See also C. Zingaretti, R. DeFrancesco, and S. Abrignani, "Why is it so Difficult to Develop a Hepatitis C Virus Preventive Vaccine?," *Clinical Microbiology and Infection*, vol. 20, supp. 5 (2014): 103-109.

[5]See Centers for Disease Control and Prevention "*Who Should NOT Get Vaccinated with these Vaccines?,*" accessed April 18th, 2023, https://www.cdc.gov/vaccines/vpd/should-not-vacc.html#print.

[6]The National Defense Authorization Act for Fiscal Year 2017 called for the development of a national biodefense strategy. See Pub. L. No. 114-328, § 1086, 130 Stat. 2000, 2423 (2016) (codified at 6 U.S.C. § 104). In 2018, the White House first issued the *National Biodefense Strategy*, and the 2022 *National Biodefense Strategy and Implementation Plan* updates the 2018 strategy.

[7]As defined by the *National Biodefense Strategy and Implementation Plan*, biological incidents are (1) any natural or accidental occurrence in which a biohazard harms humans, animals, plants, or the environment; (2) a crime involving a biohazard; or (3) any act of biological warfare or terrorism. *National Biodefense Strategy and Implementation Plan*, Annex II, §§ 3.5.2, 3.6.V.

[8]Specifically, the act requires us to monitor and oversee the federal government's efforts to prepare for, respond to, and recover from the pandemic. Pub. L. No. 116-136, § 19010(b), 134 Stat. 281, 580 (2020). The American Rescue Plan Act of 2021 also includes a provision for us to conduct oversight of the COVID-19 response. Pub. L. No. 117-2, § 4002, 135 Stat. 4, 78. All of our reports related to the COVID-19 pandemic are available on our website at https://www.gao.gov/coronavirus.

deficiencies in HHS's ability to perform its leadership role that have persisted for more than a decade.[9]

This technology assessment discusses antiviral drugs for pandemic pathogens and some of the existing and emerging technologies that could be used for drug development in advance of a pandemic. It also discusses economic challenges hindering their development and identifies policy options that could be used to promote the availability of antiviral drugs to address potential pandemic pathogens.

To address these objectives, we convened a meeting of experts in October 2022 to discuss the science and economics of antiviral drug development. We also interviewed stakeholders, scientists, and economists with expertise in the science and economics of antiviral drug development. We reviewed literature on antiviral drug development and drug development technology more broadly. Additionally, we reviewed literature on the impact of economic incentives on antiviral drug development as well as strategies for overcoming challenges. See appendix I for a full discussion of our objectives, scope, and methodology, and see appendix II for a list of the experts who participated in the October 2022 meeting.

We conducted our work from February 2022 through September 2023 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. This 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 the findings and conclusions in this product.

[9]See GAO, *High-Risk Series: Efforts Made to Achieve Progress Need to Be Maintained and Expanded to Fully Address All Areas,* GAO-23-106203 (Washington, D.C.: Apr. 20, 2023).

# 1 Background

## 1.1 Pandemics risk human health and economic stability

Pandemics impose large human and economic costs on society. During the Great Influenza Pandemic of 1918–1920, an estimated 40 million people, or 2.1 percent of the global population, died and gross domestic product (GDP) fell by an estimated six percent.[10] The World Health Organization (WHO) estimates there have been almost 7 million deaths worldwide due to the COVID-19 pandemic, and by 2024, the pandemic will have reduced global economic output by an estimated $13.8 trillion relative to pre-pandemic forecasts, according to an International Monetary Fund paper.[11] The Congressional Research Service has reported that the COVID-19 pandemic pushed the U.S. GDP growth rate down to negative 9 percent in the second quarter of 2020 compared with the previous quarter—the largest quarterly decline in U.S. GDP in 70 years.[12] Pandemics also have other costs. For example, we have reported that the COVID-19 pandemic imposed significant learning losses among school-age children.[13] Additionally, the WHO estimates that the COVID-19 pandemic triggered a 25 percent increase in major depressive and anxiety disorders globally in 2020.[14]

Researchers estimate that global economic losses from potential future pandemics would average more than $800 billion dollars annually. This annualized loss is based on estimates of the likely frequency and intensity of pandemics as well as estimates of mortality, economic output, and learning losses from pandemics of varying severities.[15] While these estimates do not include the full range of economic costs from pandemics, they highlight the damage that such events may bring and the potential value of preparatory actions to mitigate these significant costs.

We have also reported that most pandemics with known origins were caused by the natural transmission of a virus through animal-to-human contact and that outbreaks have also been reported as a result of

[10]GDP measures the monetary value of all final goods and services in a country in a given period of time, such as a year. Researchers estimate that if pandemic similar to the Great Influenza Pandemic of 1918–1920 occurred today, it would result in 150 million deaths worldwide. See Robert J. Barro, José F. Ursúa, and Joanna Weng, *The Coronavirus and the Great Influenza Pandemic: Lessons from the "Spanish Flu" for the Coronavirus's Potential Effects on Mortality and Economic Activity*, Working Paper 26866 (Cambridge, Mass.; National Bureau of Economic Research, 2020).

[11]Agarwal, Ruchir et al., "A Global Strategy to Manage the Long-Term Risks of COVID-19," *IMF Working Papers*, no. 068 (2022).

[12]Congressional Research Service, *Global Economic Effects of COVID-19: Overview*, CRS R46270 (Washington, D.C.: 2022).

[13]See GAO, *Pandemic Learning: Less Academic Progress Overall, Student and Teacher Strain, and Implications for the Future*, GAO-22-105816 (Washington, D.C.: June 8, 2022).

[14]Loneliness; fear of infection, suffering and death for oneself and for loved ones; grief after bereavement; and financial worries have been cited as stressors leading to higher rates of anxiety and depression. See World Health Organization, *Mental Health and COVID-19: Early Evidence of the Pandemic's Impact: Scientific Brief*, WHO/2019-nCoV/Sci_Brief/Mental_health/2022.1 (March 2, 2022).

[15]Rachel Glennerster, Christopher M. Snyder, and Brandon Joel Tan, *Calculating the Costs and Benefits of Advance Preparations for Future Pandemics*, Working Paper 30565 (Cambridge, Mass.: National Bureau of Economic Research, 2022).

laboratory accidents.[16] Scientific literature suggests that the likelihood of disease spillover from animals has risen because of factors such as increases in human-animal interactions through farming practices, wildlife trade, habitat loss, and climate change. All of these factors could increase the probability and frequency of pandemics in the future. Despite concerns about drug-resistant bacteria or fungal pathogens, a team at Johns Hopkins University found that viruses are most likely to be the source of the next pandemic because of some viruses' ability to spread rapidly from person to person and because there are fewer existing treatment options for viruses.[17]

## 1.2 Antiviral drugs target viral functions and vary in the range of pathogens they treat

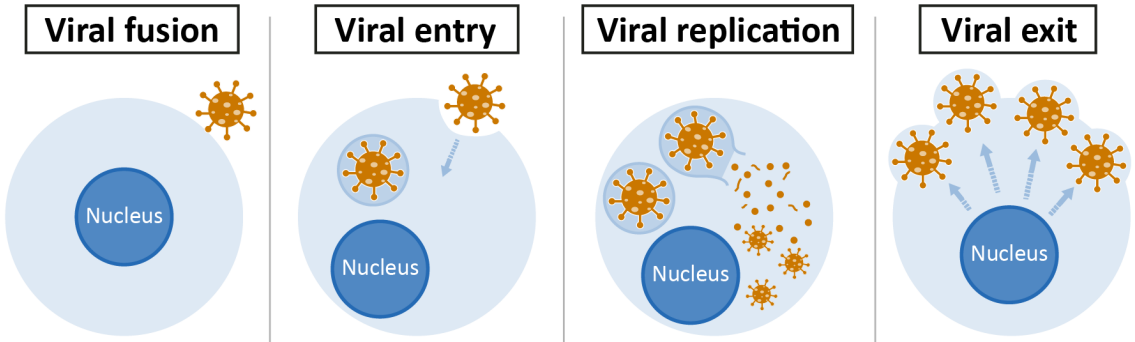
Antiviral drugs help the body fight off harmful viruses. They can ease symptoms and shorten the length of an infection and, in some instances, may lower the risk of acquiring or spreading viral infections. These drugs can be divided into subcategories based on, among other things, whether they are small- or large-molecule drugs, whether they affect the virus or the host cell, and how they produce an effect, known as the mechanism of action. These distinctions affect whether and to what extent antiviral drugs will be effective in treating different viruses or viral families.

The viral life cycle can differ between viruses, but the cycle follows the same basic stages: (1) attachment to a cell, (2) entry into a cell, (3) replication inside a cell to create new viruses, and (4) exit of new viruses from the cell to infect other cells (see fig. 1). Antiviral drugs can target various stages of the viral life cycle, depending on their mechanism of action. For example, antiviral drugs whose mechanism of action prevents the virus from attaching to a cell are referred to as fusion inhibitors. These fusion inhibitors can be classified into those that can affect the virus by binding to the part of the virus that attaches to a host cell or those that can affect the host cell by binding to the receptor sites on the host cell, thereby preventing the virus from attaching to the cell.

[16]See GAO, *Pandemic Origins: Technologies and Challenges for Biological Investigations*, GAO-23-105406 (Washington, D.C.: Jan. 27, 2023).

[17]According to the Johns Hopkins Center for Health Security, several attributes are likely to be essential components of any pathogen that poses a global catastrophic biological risk. These attributes include efficient human-to-human transmissibility, an appreciable case fatality rate, the absence of an effective or widely available medical countermeasure, an immunologically naïve population, virulence factors enabling immune system evasion, and respiratory mode of spread. Although most classes of microbe could evolve or be manipulated in ways that would cause a catastrophic risk to humans, viruses—especially RNA viruses—are the most likely class of microorganism to have this capacity. See Amesh Adalja et al., *The Characteristics of Pandemic Pathogens* (Johns Hopkins Bloomberg School of Public Health, Center for Health Security, 2018).

**Figure 1: An example of the SARS-CoV-2 viral life cycle**




Source: GAO analysis; GAO (icons). | GAO-23-105847

Antiviral drugs work differently depending on the drug and virus type. Further, classes of antiviral drugs that use the same mechanism of action may affect different viruses differently. Experts we spoke with agreed that development of a wide range of antiviral drugs with different mechanisms of action could address a wide range of pathogens and address the uncertainty about which pathogens may cause a future pandemic.

### 1.2.1 Small-molecule antiviral drugs

Experts concurred that small-molecule antiviral drugs are amenable to early development in advance of a pandemic.[18] Most of these drugs can be administered orally, can pass through cell membranes to reach intracellular targets, and may be active against many different viruses. They can inhibit specific processes that a virus uses during its life cycle.

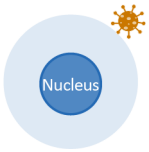
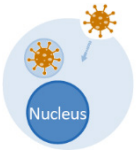
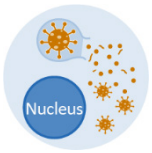
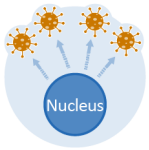
Different small-molecule antiviral drugs can use different mechanisms of action and work at different stages of the viral lifecycle. For example, researchers could develop a drug that mimics a portion of the virus's genetic material, which would inhibit the virus's ability to replicate inside the host cell. A drug's mechanism of action could also block a virus from exiting a host cell after replication, which would prevent it from infecting other cells (see table 1).[19] Understanding the

[18] A small-molecule antiviral drug is a drug that can enter cells easily because it has a low molecular weight.

[19] In some cases, antiviral drug combinations with several mechanisms of action can be useful. Currently, the standard treatment for HIV infection entails the use of three or more antiviral medicines, sometimes referred to as an anti-HIV cocktail. The goal of this therapy is to reduce the amount of virus in the body to a level that can no longer be detected.

mechanism of action of a drug is a fundamental way of understanding how a drug acts on the human body, and it provides information regarding a drug's appropriate use and possible side effects.

**Table 1: Antiviral drugs, by viral life cycle stage and examples of mechanism of action**

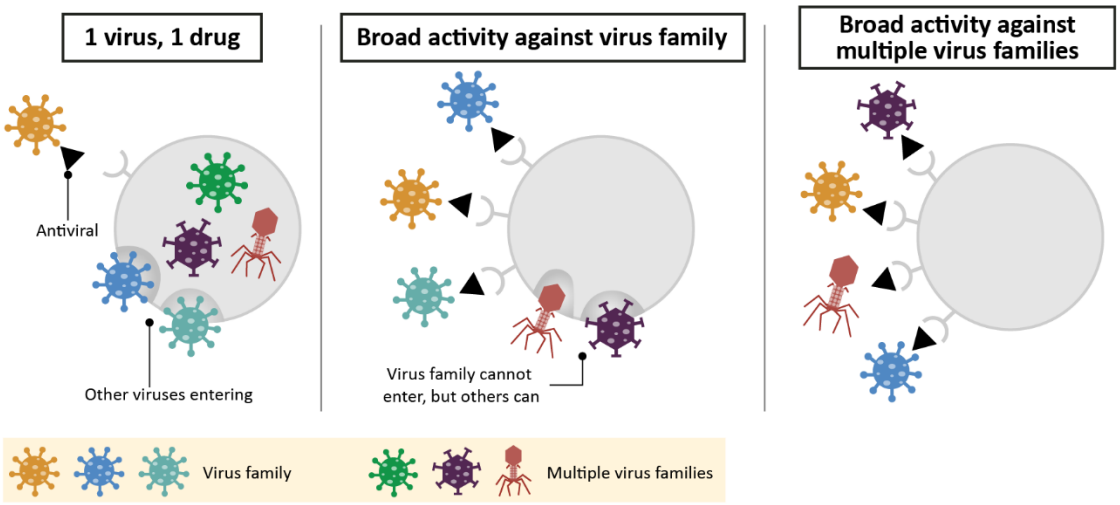
| Stage | Drug using this mechanism of action (generic name) | Mechanism(s) of action | Pathogen |
|---|---|---|---|
| **Fusion**   | Enfuvirtide | Fusion inhibitor – Binds to a spike protein on the virus to inhibit viral fusion. | HIV |
| | Maraviroc | Fusion inhibitor – Binds to a receptor on the host cell to inhibit viral fusion. | HIV |
| **Entry**   | Amantadine | Entry inhibitor – Inhibits the protein responsible for releasing the viral genetic material inside the host cell. | Influenza A |
| **Replication**   | Remdesivir[a] | Nucleoside analog – Has structure similar to the molecular building blocks of DNA and RNA. When a virus incorporates the nucleoside analog molecule, viral replication is disrupted and the virus can no longer multiply. | SARS-CoV-2 |
| | Nirmatrelvir | Protease inhibitor – Inhibits the virus from processing a protein required for viral replication. | SARS-CoV-2 |
| **Exit**   | Oseltamivir | Exit inhibitor - Blocks the protein that allows for the release of newly assembled virus copies from the host cell. | Influenza A & B |
| | Tecovirimat | Exit inhibitor – Blocks the protein that allows for the release of newly assembled virus copies from the host cell. | Smallpox (also being used to treat mpox[b]) |

Source: GAO analysis of Department Health and Human Services (HHS) documentation; GAO (icons). | GAO-23-105847

[a]Remdesivir is a drug compound.
[b]On November 28, 2022, the Centers for Disease Control and Prevention adopted the term "mpox" to refer to the disease previously referred to as "monkeypox" in support of recommendations by the World Health Organization and HHS.

Small-molecule antiviral drugs may be effective against one pathogen, a broad spectrum of viruses within a family, or a broad spectrum of viruses across viral families depending on their mechanism of action (see fig. 2).

**Figure 2: Virus-specific versus broad-spectrum antiviral drugs**




Source: GAO analysis; GAO (icons). | GAO-23-105847

Antiviral drug development has focused on virus-specific approaches, identifying a specific viral protein as a drug target, and attempting to increase the drug's efficacy while limiting potential toxicity.[20] Virus-specific drug development can be simpler than the more complex design of broad-spectrum antiviral drugs, which often requires targeting critical proteins or cellular processes used by different viruses.[21] Broad-spectrum antiviral drugs can be classified into two main categories: (1) host-targeted antiviral drugs that stimulate the immune system or target host (e.g., human) cell processes required for viral replication and (2) drugs that target the viruses directly. Both present advantages and disadvantages (see table 2).

[20]In this report, "efficacy" refers to the results of adequate and well-controlled clinical trial studies and "effectiveness" refers to the results of studies carried out under field or "real-world" conditions.

[21]Because broad-spectrum antiviral drugs target an entire virus family or multiple virus families, they have the potential to treat infections caused by different viruses.

**Table 2: Pros and cons of various antiviral drug strategies**

| | Virus-specific antiviral drug strategies | Broad-spectrum antiviral drug strategies | |
|---|---|---|---|
| | | Host targeted | Virus targeted |
| **Pros** | • Proven efficacy<br>• Easier to design, one viral target | • Demonstrated antiviral effect<br>• Higher barrier to drug resistance | • Less potential for toxicity than host-targeted strategies<br>• Potential for repurposing against other viruses |
| **Cons** | • Low barrier to drug resistance<br>• Long development time | • Potential for toxicity | • More complex design<br>• Few examples of broad-spectrum antiviral drugs ((e.g., remdesivir, cidofovir & favipiravir) |

Source: Geraghty, R.J.; Aliota, M.T.; Bonnac, L.F. Broad-Spectrum, Antiviral Strategies and Nucleoside Analogues. Viruses 2021, 13, 667. | GAO-23-105847

Because broad-spectrum antiviral drugs can treat multiple viruses, they could be particularly valuable in preparing for pandemics where the specific viral threat is unknown. Some researchers have found that broad-spectrum antiviral drugs are effective against multiple viruses in the same family or multiple families of viruses that could cause pandemics and that these drugs could be rapidly deployed to prevent or mitigate future pandemics.[22] For example, tecovirimat, an antiviral drug developed to treat smallpox, is currently being used to treat individuals infected with mpox.[23] According to the Centers for Disease Control and Prevention (CDC), because the viruses that cause mpox and smallpox are similar, antiviral drugs developed to protect against smallpox may be used to treat mpox.[24]

### 1.2.2 Large-molecule antiviral drugs—monoclonal antibodies

In addition to small molecule drugs, large-molecule drugs can be used to treat infectious diseases. These include monoclonal antibodies, which are laboratory-produced proteins that mimic the antibodies naturally produced by the human immune system (see fig. 3). Monoclonal antibodies can be used as a treatment for or prevention of viral infections and their effect can last from weeks to months. In contrast to small-molecule antiviral drugs, monoclonal antibodies are more complex and costly to develop. One method of creating monoclonal antibodies is to use blood from individuals who have recovered from an infection. Scientists then extract antibodies from blood and replicate

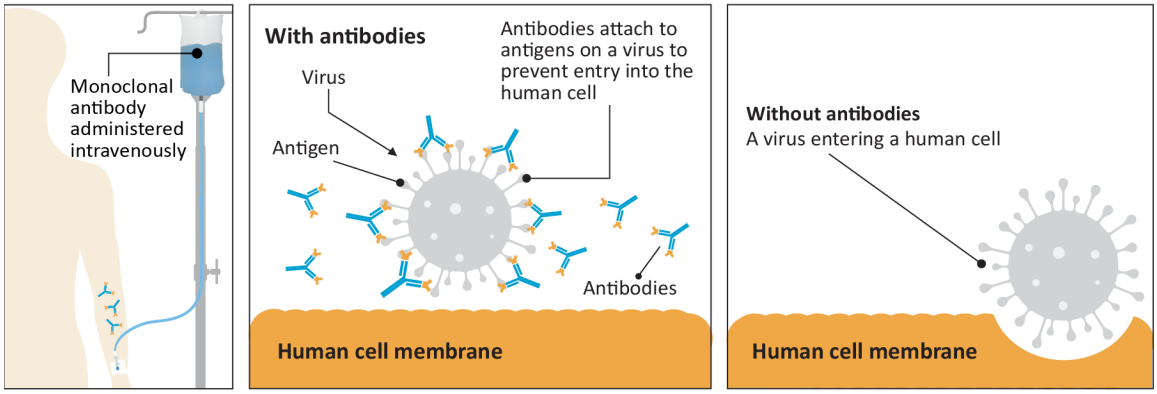
[22]Gustavo Garcia Jr., Joseph Ignatius Irudayam, et al. "Broad-spectrum antiviral inhibitors targeting pandemic potential RNA viruses," bioRxiv [Preprint] (Jan. 20, 2023), https://doi.org/10.1101/2023.01.19.524824

[23]Tecovirimat is an exit inhibitor. It prevents the development of a protein that allows the newly created viruses within an infected cell from exiting the cell.

[24]Smallpox is an acute contagious disease caused by the variola virus, a member of the poxviridae family. Mpox is also a member of the poxviridae family, which also includes vaccinia virus, the cowpox virus, and several other viruses. Common symptoms of mpox are rash, fever, sore throat, headache, muscle aches, back pain, low energy, and swollen lymph nodes.

and manufacture them in large quantities.[25] While monoclonal antibodies can be rapidly developed and can treat diseases like COVID-19, when new variants of viral pathogens emerge, they can lose their efficacy.[26] They are also complex to manufacture and must be stored at cold temperatures. However, HHS officials said monoclonal antibodies have a well-defined regulatory approval pathway, and if they can be developed and used early in a pandemic, they could provide some initial or long-term benefit, as was the case early in the COVID-19 pandemic.[27]

**Figure 3: Example of monoclonal antibody targeting SARS-CoV-2, the virus that causes COVID-19**




Source: GAO (analysis); Maryland Department of Health Office of Preparedness and Response (information); GAO, iiierlok_xolms/stock.adobe.com (icons). | GAO-23-105847

[25]According to HHS, the need for blood from those who have been exposed to a new pathogen can be overcome by vaccinating "humanized" animals and isolating fully human monoclonal antibodies from their blood.

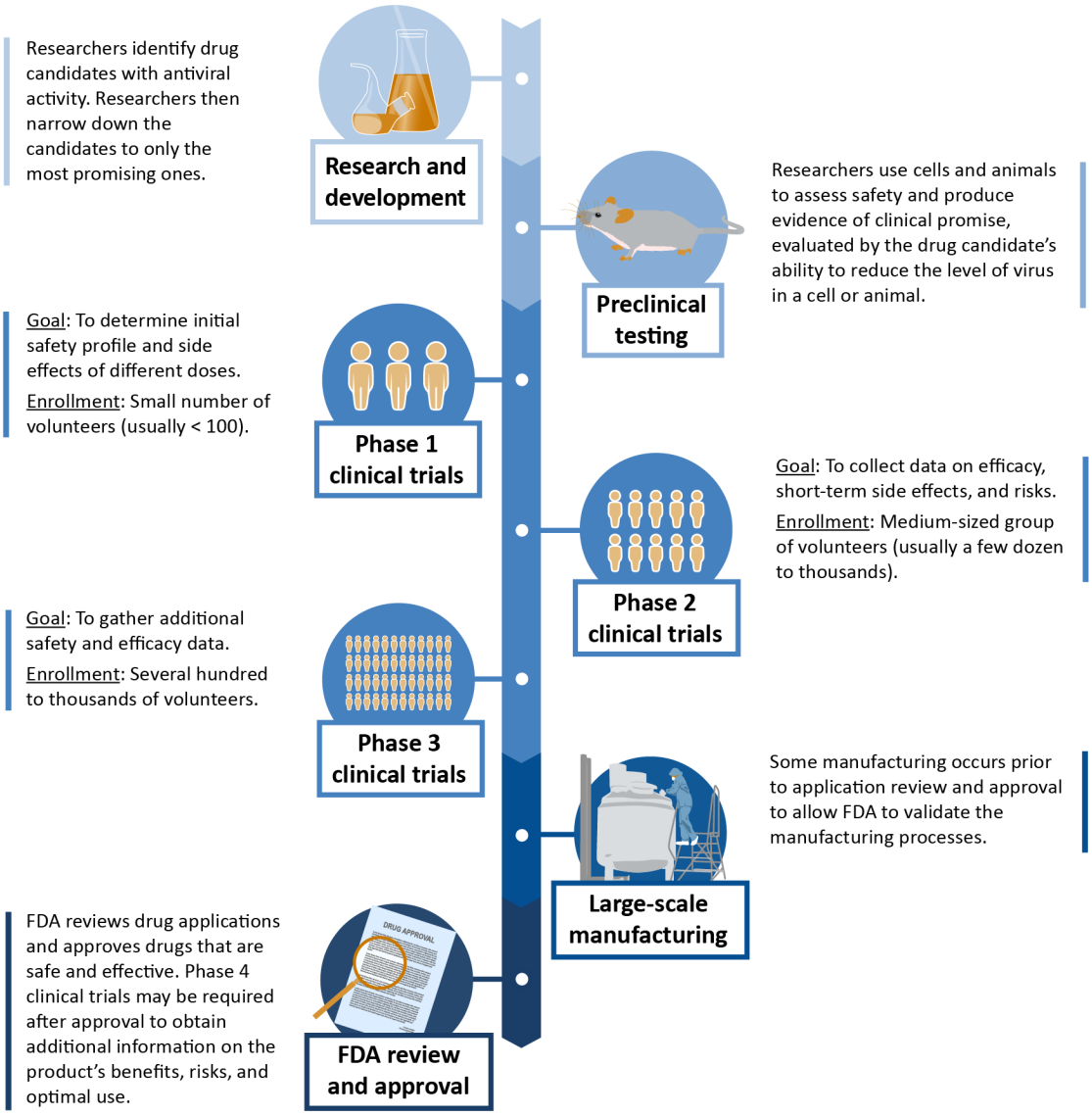
[26]FDA may temporarily allow the use of unapproved medical products, or unapproved uses of approved products, through issuance of an emergency use authorization, provided certain statutory criteria are met. See 21 U.S.C. § 360bbb-3. Since the start of the COVID-19 pandemic, the FDA has granted emergency use authorization for seven monoclonal antibody treatments for COVID-19. As of March 20, 2023, five of these are no longer authorized in any U.S. region due to the high frequency of circulating SARS-CoV-2 variants that are not susceptible to these monoclonal antibodies. One of the emergency use authorizations was revoked in April 2021.

[27]Researchers reported that it usually takes approximately 12 months from initial monoclonal antibody research to an investigational new drug application, although this can be faster in a pandemic.

## 1.3 Antiviral drug development is expensive, time-consuming, and risky

FDA is responsible for ensuring the safety and effectiveness of medical products marketed in the U.S. While the process varies by product type, the process for drugs and biologics generally includes FDA's review of evidence submitted by a product's sponsor (typically the product developer) to determine whether the new product is safe and effective for its intended use or uses. This process usually consists of the stages highlighted in figure 4.

**Figure 4: Overview of drug development process**




Source: GAO analysis of information from the Food and Drug Administration (FDA); GAO (icons). | GAO-23-105847

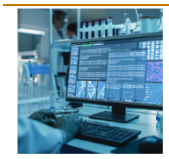
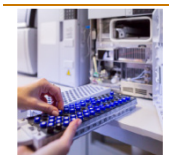
Note: In this figure, we use the term "drug" to refer to both drugs and biologics and the term "approval" to refer to both drug approval and biologic licensure. Although depicted in a linear fashion, the stages in this figure may overlap.

As for most drugs, developing and approving a new antiviral drug is a long and costly process that can take 10 or more years and involve multiple private and public entities. Estimates of the cost of development of new antiviral drugs range from $800 million to more than $2.5 billion.[28] Approximately nine out of 10 drug candidates that enter clinical trials will fail during clinical trials.

## 1.4 Technology and process innovations can reduce the risk and cost of drug development

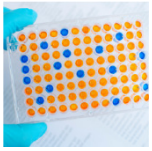
A number of new technological and process innovations may make drug development faster, less costly, and safer (see table 3). For example, researchers could use machine learning and other computational techniques to prioritize compounds for further testing, rather than conducting an expensive screen of many compounds in the laboratory.[29] This also decreases the biosafety risks associated with handling potential pandemic pathogens in a laboratory.

**Table 3: Examples of technology and process innovations currently used for antiviral drug development**

| | Technology and description |
|---|---|
|  | **Artificial intelligence and machine learning** can be used to help researchers identify new drug targets, screen known compounds for new therapeutic applications, and design new drug candidates. They can also be used to augment preclinical testing to predict toxicity before testing potential drugs in humans. |
|  | **Organ chips** are systems containing miniature tissues that mimic human physiology and are used in preclinical studies. They reduce the expense and risk associated with testing drugs in animals or humans. |
|  | **High-throughput screening** uses automated systems to simultaneously run assays, or biological tests, on large numbers of compounds. Pharmaceutical companies often have large, proprietary collections of compounds known as chemical libraries for screening. The main goal of high-throughput screening is to accelerate drug discovery by screening large compound libraries at a rate that may exceed a few thousand compounds per day. |

[28]Drug development costs tend rise in each successive phase of development, such as phase 3 clinical trials. See Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics*, vol. 47 (2016): 20-33. A more recent study found that the median investment to bring a new drug to market was about $1.1 billion; see Olivier J. Wouters, Martin McKee, and Jeroen Luyten, "Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018," *Journal of the American Medical Association*, vol. 323, no. 9 (2020): 844–853.

[29]See GAO, *Artificial Intelligence in Health Care: Benefits and Challenges of Machine Learning in Drug Development,* GAO-20-215SP (Washington, D.C.: Dec. 30, 2019).

| | Technology and description |
|---|---|
|  | **Standardized assays** are standardized tests that can be used by different antiviral drug developers to allow them to measure responses to drugs in the same way, which allows a common comparison of drug candidates. For example, standardized assays could measure the level of antibodies in clinical trial participants who have received different antiviral drug candidates. |
|  | **A common control group** allows multiple groups of participants in a clinical trial to be compared with a single control group—a group that has received a placebo. This approach allows a comparison of the effects of multiple antiviral drug candidates simultaneously and reduces the number of clinical trial participants needed overall. |
|  | **Virtual clinical trials**, also referred to as decentralized trials, use wearable digital technologies to collect participant data. This approach extends the reach of clinical investigations to where patients live and work through the use of digital health technologies including watches, bracelets, patches, textiles, and clothing. This can be faster and cheaper than having participants physically come into a health care facility for monitoring. |

Sources: GAO (analysis); Gorodenkoff/luchschenF/Sodel Vladyslav/oatawa/jarun011/nuruddean/stock.adobe.com (images top to bottom). | GAO-23-105847

## 1.5 HHS conducts efforts to support antiviral drug development

Within HHS, the National Institutes of Health (NIH) and the Administration for Strategic Preparedness and Response (ASPR) have played key roles in the development of medical countermeasures, such as antiviral drugs and vaccines for infectious disease outbreaks.

**Within NIH**, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Center for Advancing Translational Sciences (NCATS) support antiviral drug development by funding research and providing drug discovery tools and technologies to drug researchers. NIAID and NCATS typically support earlier stages of antiviral drug development, which includes basic research and development, animal studies, and early stage clinical trials;[30]

**Within ASPR**, the Biomedical Advanced Research and Development Authority (BARDA) funds all parts of advanced research and development for medical countermeasures, which includes vaccines and therapeutics, including clinical trials, and manufacturing development. BARDA's annual funding is currently limited to pandemic influenza and chemical, biological, radiological, and nuclear threats in which a Material Threat

[30]NIH supports clinical trial networks for developing pandemic vaccines and therapeutics and contributed to the Accelerating COVID-19 Therapeutic Interventions and Vaccines Program in response to the COVID-19 pandemic. According to NIH, the Advanced Research Projects Agency for Health supports the development of high-impact research to drive biomedical and health breakthroughs to deliver transformative, sustainable, and equitable health solutions.

Determination exists.[31] BARDA supports all stages of development, from early preclinical development to later stage research and development, such as clinical trials.[32] For example, BARDA has supported later stage antiviral drug development for pandemic influenza, smallpox, and COVID-19.

In June 2021, HHS launched the Antiviral Program for Pandemics (APP), which aims to identify antiviral drugs that target SARS-CoV-2 and other viruses with pandemic potential. According to NIH, APP is intended to accelerate the development of a portfolio of antiviral drugs that can help combat future pandemics and takes an interagency approach to antiviral drug development.

To support APP efforts, in May 2022, NIH established nine multidisciplinary Antiviral Drug Discovery Centers for Pathogens of Pandemic Concern, located at multiple existing academic health centers and research institutions. HHS officials said that the centers are currently funded through fiscal year 2025. According to NIH officials, anticipated future funding has been removed and the program is winding down, resulting in a negative impact on current research activities.

[31]BARDA officials noted that funding used to develop capabilities for pathogens with a material threat determination can also be used to address other threats without such a determination. The Secretary of Homeland Security is required to assess current and emerging threats from chemical, biological, radiological, and nuclear agents on an ongoing basis and determine which agents present a material threat against the United States sufficient to affect national security. Using these material threat determinations, the Secretary of Health and Human Services is required to assess potential public health consequences of exposure to agents and determine which medical countermeasures are necessary to protect public health. 42 U.S.C. § 247d-6b(c)(2)(A) and (B).

[32]BARDA typically supports preclinical development through its Division of Research, Innovation and Ventures (DRIVe), Blue Knight, DRIVe accelerators, and CARB-X.

# 2 Factors Impacting the Efficient Functioning of Markets Can Lead to Limited Investment in Pandemic Antiviral Drugs

According to HHS officials, few drugs are currently available to treat pathogens from viral families that NIAID has identified as having the potential to cause future pandemics. Experts we spoke to believed that market failures have led to limited investment in pandemic antiviral drugs. Further market failures and other market factors have limited investments in manufacturing capacity to produce these drugs.

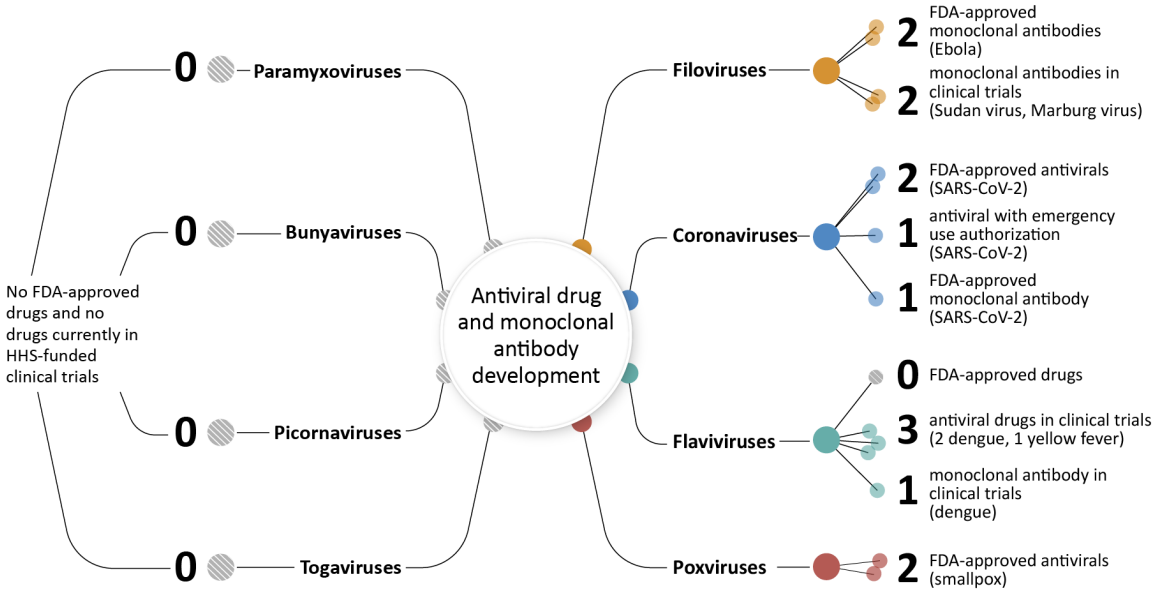
## 2.1 Few antiviral drugs currently exist and the market currently produces less than would be socially beneficial for future pandemics

According to HHS officials, there are currently few approved drugs to treat pathogens from viral families that NIAID has identified as having the potential to cause future pandemics.[33] As of May 2023, these include two monoclonal antibodies for filoviruses (Ebola), two small-molecule antiviral drugs for smallpox, and one monoclonal antibody and two small molecule drugs for SARS-CoV-2.[34] In addition, there are two monoclonal antibodies currently in clinical trials for filoviruses (Sudan virus and Marburg disease), three small molecule antiviral drugs in clinical trials for flaviviruses (two for dengue and one for yellow fever), and one monoclonal antibody in clinical trials for one flavivirus (dengue). There are no approved drugs currently available or in NIAID- or BARDA-funded clinical trials for paramyxoviruses, bunyaviruses, picornaviruses, or togaviruses, although there are ongoing discovery efforts funded by NIH to identify drugs for these and other viruses. See figure 5.

[33]According to NIAID, viral families with high potential to cause a pandemic in the future include paramyxoviruses, coronaviruses, bunyaviruses, togaviruses, filoviruses, picornaviruses, and flaviviruses. In addition, ASPR officials noted that influenza viruses are also among those most likely to cause a pandemic and BARDA is conducting one clinical trial on an antiviral drug for influenza.

[34]The monoclonal antibody for SARS CoV-2 is a host-directed treatment, rather than an antiviral.

**Figure 5: State of drug development for viral families with high potential to cause future pandemics as of May 2023**




FDA = U.S. Food and Drug Administration
HHS = Department of Health and Human Services

Source: GAO analysis of HHS and other documentation; GAO (icons). | GAO-23-105847

Note: Clinical trials are tests done to see if a product, such as an antiviral drug, is safe and effective, according to the National Institutes of Health. This graphic refers to clinical trials funded by the National Institute of Allergy and Infectious Diseases or the Biomedical Advanced Research and Development Authority. One study found that the average length of time from the start of clinical trials to marketing is about 7.5 years and that the entire process from discovery to registration with the Food and Drug Administration (FDA) takes 10 to 15 years for a typical drug.[35] Monoclonal antibodies are laboratory produced proteins that mimic the antibodies naturally produced by the human immune system and their effect can last from weeks to months. Researchers reported that it takes approximately 12 months from initial monoclonal antibody research to an investigational new drug application, although this can be faster in a pandemic.

Experts we spoke with believed that certain types of market-disrupting factors have led to limited investment in pandemic antiviral drugs; some of these are known as market failures. Market failures occur when dynamics in a market lead to outcomes that fall short of what would have been ideal or would have maximized benefits to society as a whole. In the case of drugs for pandemics, market failures occur when prices of pandemic drugs do not rise to levels that would induce developers to supply the socially desired quantity of such drugs.[36] This leads to drug developers producing fewer drugs for pandemic pathogens even though the social benefits from additional drugs are high. This,

[35]Aylin Sertkaya, Anna Birkenbach, Ayesha Berlind, and John Eyraud, *Examination of Clinical Trial Costs and Barriers for Drug Development* (Washington, D.C.: Department of Health and Human Services, July 25, 2014).

[36]In many circumstances, market prices can provide valuable information to producers about what consumers value. This information can therefore guide producers' investments in products.

in other words, is a market failure (see text box).

**Market failures in pandemic drug development.** Economists we spoke with identified three factors that can cause market failure and, therefore, hinder the development of socially beneficial pandemic drugs.

- **Pricing constraints.** During a pandemic, drug developers anticipate that political and social constraints on pricing will reduce their returns on investment. While these pricing constraints aim to allow broad accessibility of such products to the public, they substantially reduce private incentives in developing pandemic drugs.
- **Positive externalities.** By curbing the pathogen's transmission, some pandemic drugs create benefits for the broader public, even those not taking the drug, known as "spillover" benefits. For example, antiviral drugs can reduce the amount of virus in an infected person's body, and the likelihood that they will spread the infection to others. However, developers cannot charge higher prices for these extra, or "spillover," benefits.
- **Knowledge as a public good.** A significant portion of scientific knowledge about pandemic pathogens and the technologies underlying drug development is publicly available, such as through published research. Developers cannot exclude the public from accessing this information even though the public is not paying for research and development costs. The public availability of information related to pandemic drugs reduces private sector incentives to invest in this research, because developers prefer to wait for others to undertake initial actions in this space ("free-ride"). However, when the private sector waits on others to make initial investments, the result is collectively fewer investments in this public good than would benefit society.

Source: GAO analysis. | GAO-23-105847

Other market factors also limit or complicate investment in pandemic antiviral drugs. Antiviral drugs for pathogens that may cause future pandemics but that do not currently pose a public health risk face uncertain market demand, exacerbating market failures discussed above. According to experts, there are limited financial incentives for the private sector to invest in therapeutic antiviral drugs for future pandemics because the timing and scale of demand for such products is very difficult to predict. For drug developers, this market uncertainty may shift incentives away from unknown potential future pandemic threats and toward known diseases with existing markets. For example, if developers are deciding between developing drugs for a potential future pandemic or drugs for which a known market and revenue stream exists, such as a cancer drug, they will choose to invest in the cancer drug. According to experts, investments in drugs with existing markets are easier to justify to shareholders because it is more likely that revenue will be realized before the drug developer loses patent protection or other marketing exclusivities.[37] In other words, patents on drugs for potential future pandemics may expire by the time a pathogen emerges and the drug is needed, resulting in a negative return on investment.

## 2.2 Antiviral drug manufacturing capacity would likely be strained in the event of a pandemic

In addition to limiting investment in initial research and development for pandemic antiviral drugs, market failures and other market factors also limit investment in manufacturing capacity to produce them. For example, industry officials and experts told us

[37]The U.S. Patent and Trademark Office reviews patent applications, including those from drug developers. If the office grants a patent, other drug companies are excluded from making, using, or selling the patented product during the life of the patent, generally 20 years. In addition to patent protections, some approved drugs may be also eligible for certain periods of market exclusivity, which may delay FDA's approval of competing drug products. Market exclusivity begins only upon FDA approval of a drug, whereas patents can be issued or expire at any time, regardless of a drug's approval status. Patents and periods of market exclusivity may or may not run concurrently, depending on the circumstances.

that in the event of a pandemic that required production of antiviral drugs for a large portion of the U.S. population, it is unlikely that existing antiviral drug manufacturing capacity would be sufficient. Further, while some domestic and international manufacturing capacity currently exists, experts stated that (1) investments lagged in newer manufacturing technologies which can enable the rapid production of antiviral drugs in a pandemic, and (2) manufacturers may be unable to shift production from nonpandemic to pandemic drugs.[38] In addition, generic drug manufacturers that may have some extra capacity generally experience narrow profit margins on these drugs, which reduces their incentive to establish and maintain substantial spare manufacturing capacity.[39]

Experts also said that domestic availability of drugs often relies on international supply chains for ingredients used in manufacturing drugs. A majority of active pharmaceutical ingredients and chemical compounds for critical medicines are located abroad.[40] Pandemics can disrupt supply chains, and disruptions may occur at the same time that demand for pandemic antiviral drugs, vaccines, and other drugs increases, leading to shortages. These shortages create strong incentives for countries to limit the flow of ingredients across international borders, creating risks that existing supply chains may not be able to deliver ingredients during a pandemic.

[38]We have reported on how the lack of a commercial market for medical countermeasures, including antiviral drugs and vaccines, used in response to low-probability, high-consequence events may reduce incentives for large pharmaceutical companies to invest consistently in these products, instead of others that may be more profitable. 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.: Mar. 31, 2014); GAO, *Public Health Preparedness: HHS Should Plan for Medical Countermeasure Development and Manufacturing Risk*, GAO-23-105713 (Washington, D.C.: Feb. 2, 2023).

[39]We have reported that the narrow profit margins of generic drugs make it difficult for drug manufacturers to make the business case for adopting other technologies that could increase manufacturing capacity. See GAO, *Drug Manufacturing: FDA should Fully Address Its Efforts to Encourage Innovation*, GAO-23-105650 (Washington, D.C.: Mar. 10, 2023).

[40]Active pharmaceutical ingredients include, among other things, drug components intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. See 21 C.F.R. § 207.1 (2022). The United States and others rely on a global supply chain for pharmaceuticals and ingredients. These flows were vulnerable during the COVID-19 pandemic, as national and international responses disrupted the production and shipping of certain pharmaceuticals and components around the world because of lockdowns, understaffing, and travel and export bans. See: Mariana P. Socal, Joshua M. Sharfstein, and Jeremy A. Greene, "The Pandemic and the Supply Chain: Gaps in Pharmaceutical Production and Distribution," *American Journal of Public Health,* vol. 111, no. 4 (2021): 635–639.

# 3 Mechanisms to Incentivize Antiviral Drug Development

As noted above, due to market failures, uncertainty of demand, and other factors, market forces alone will not induce the creation of pandemic drugs at a level that maximally benefits society and aids in preparedness for potential future pandemics. However, several mechanisms can be used to incentivize additional investment in antiviral drugs. These mechanisms either subsidize some portion of the development process or provide rewards for successful development of drugs.

## 3.1 Types of incentives for drug research and development

Through our literature review, past work, and interviews with economists, we identified two key types of mechanisms with the potential to incentivize pandemic drug development.[41] Policymakers in government, such as Congress or agency officials, can use interventions that can be broadly classified as "push" or "pull" incentives.

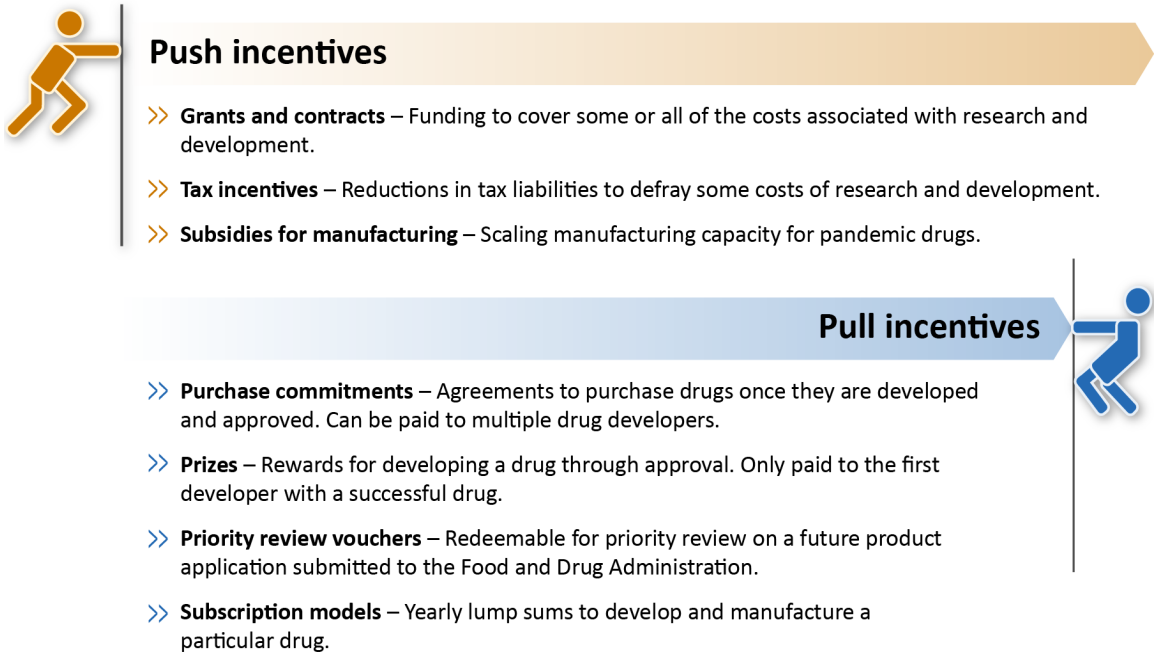
- **Push incentives** usually occur earlier in the drug development cycle and subsidize the cost of research or product development by providing grant and contract funding to academic institutions, tax credits to businesses for research and development, and funding to developers to construct or expand manufacturing capacity. The U.S. government has used push incentives, such as grants and contracts, to fund research and development for pandemic antiviral drugs such as those for COVID-19.[42]
- **Pull incentives** provide developers with a known return on investment and reward the successful development of a new drug. For example, the government can commit to purchasing a certain quantity of a drug or promise a cash prize for successful approval of a drug. Along with push incentives, the U.S. government also used pull incentives to spur the development of COVID-19 vaccines and antiviral drugs, as well as other medical countermeasures for pathogens that present biological threats.

See figure 6 for additional examples of push and pull incentives.

[41]See appendix I for more information.

[42]See GAO, *Biomedical Research: Information on Federal Contributions to Remdesivir,* GAO-21-272 (Washington, D.C.: Mar. 31, 2021).

**Figure 6: Examples of push and pull incentives for drug research and development**




Source: GAO analysis; GAO (icons). | GAO-23-105847

Experts we spoke with said that some incentives work better in certain circumstances than others.[43] For example, because grants are effective at encouraging research and development, they can also encourage innovations in drug research and development technology more broadly, such as artificial intelligence or high-throughput screening. By creating knowledge as a public good, these drug development innovations can benefit the development of other types of drugs. However, experts said that grants, and push funding incentives in general, may not lead to a developed drug, because they target research only by defraying its costs and because a drug candidate may not advance to clinical trials or other later development stages.[44] Tax incentives may be useful to incentivize research in a particular area, but they are not effective for developers without tax liability. The text box describes one type of incentive—subscription models.

[43]We have previously reported on these incentives in the vaccine context. See GAO-22-104371.

[44]One expert told us that a challenge of push funding relates to developers putting forward research projects that may not be high value, because developers may be incentivized to overstate the merits of the research in order to receive funding.

**A Subscription Model for Drug Development**

Subscription models are a type of incentive payment from governments to drug manufacturers. The defining feature of a subscription model is a negotiated fixed payment to a manufacturer in exchange for a certain number of doses of one or more specific drugs over a predefined period. While subscription models may vary, the economics behind the model takes into account that the cost of developing a novel drug is mostly high and fixed and the variable cost of manufacturing a drug is relatively low. Under a traditional model, drug manufacturers would charge high drug prices to recoup those fixed costs. A subscription agreement, by contrast, would allow the manufacturer to recoup much of its fixed costs through collecting a lump-sum fee, negating the need to charge high prices per dose.

According to one expert we spoke to, the use of a subscription model for pandemic preparation would allow antiviral drug developers to receive revenue for developing antiviral drugs independent of whether a pandemic occurred or the resulting antiviral drug was used.

Source: GAO analysis. | GAO-23-105847

Pull incentives such as advanced purchase commitments can be beneficial in that they can allow drugs to be stockpiled for future use or to treat people immediately. However, advanced purchase commitments, and pull funding in general, often provide duplicate incentives to multiple firms with varying antiviral drugs for the same pathogen, each with different probabilities of success. This duplicate funding can substantially increase costs to the government, because it may ultimately purchase several different antiviral drugs.[45] While prizes must be large enough to motivate developer interest, they are usually structured so that the prize goes only to the first developer. As a result, prizes can save money because they are paid only once, when a single antiviral drug receives emergency use authorization or FDA approval.

However, prizes and advanced purchase commitments do not reduce the cost of research and development and may not ensure sufficient capacity to respond to all potential infectious disease scenarios. Such incentives do not generally include provisions for complementary investments in manufacturing capacity and may not ensure sufficient supply of drugs.

Further, experts said that the current patent system does not effectively facilitate the development and manufacturing of pandemic drugs. This is because patents may have expired by the time a pandemic occurs, so the developer may not be able to recoup the costs of producing such drugs.[46] Furthermore, during a pandemic, there can be public pressure to make the intellectual property publicly available at no cost in an effort to make such drugs accessible to everyone. Similar to the effect of a pricing constraint, this undermines the value of patents for developers.

### 3.1.1 Incentives used to develop smallpox treatment: Tecovirimat case study

Tecovirimat, a drug approved to treat smallpox and used to treat mpox, provides an example of the use of various incentives in enabling the development of an antiviral drug

[45]Pull incentives may fund some products for which the probability of success is lower and development costs are higher, resulting in overall higher costs of administering the pull incentives. On the other hand, in circumstances in which a diverse range of antiviral drugs may be more valuable, purchase commitments to multiple manufacturers, which result in multiple approved drugs, could be beneficial.

[46]The median patent life after FDA approval ranges between 10 and 14 years. See Reed F. Beall, Jonathan J. Darrow, and Aaron S. Kesselheim, "Patent Term Restoration for Top-Selling Drugs in the United States," *Drug Discovery Today*, vol. 24, no. 1 (2019): 20–25.

treatment.[47] Beginning in 2002, tecovirimat development began with (push) funding to conduct initial research and development, then support for clinical trials to demonstrate safety and effectiveness and, ultimately, support for manufacturing from NIAID and BARDA. In addition, BARDA awarded a five-year contract to purchase millions of doses of tecovirimat for the Strategic National Stockpile.[48] FDA provided additional incentives to the developer of tecovirimat by granting fast track and orphan drug designations[49] and by awarding a priority review voucher for a material-threat medical countermeasure[50] when it approved the drug. Orphan drug designation provides certain benefits to drug developers, including tax credits, waivers from certain fees, and market exclusivity for 7 years.[51] Figure 7 shows these incentives.

[47]Tecovirimat was approved to treat smallpox in adults and children on July 13, 2018. There are no FDA-approved treatments for mpox, but tecovirimat is currently available for the treatment of mpox under an expanded access protocol. Expanded access, which is sometimes referred to as "compassionate use," is the use of investigational drugs outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no satisfactory or comparable alternative treatment options. See 21 U.S.C. § 360bbb.

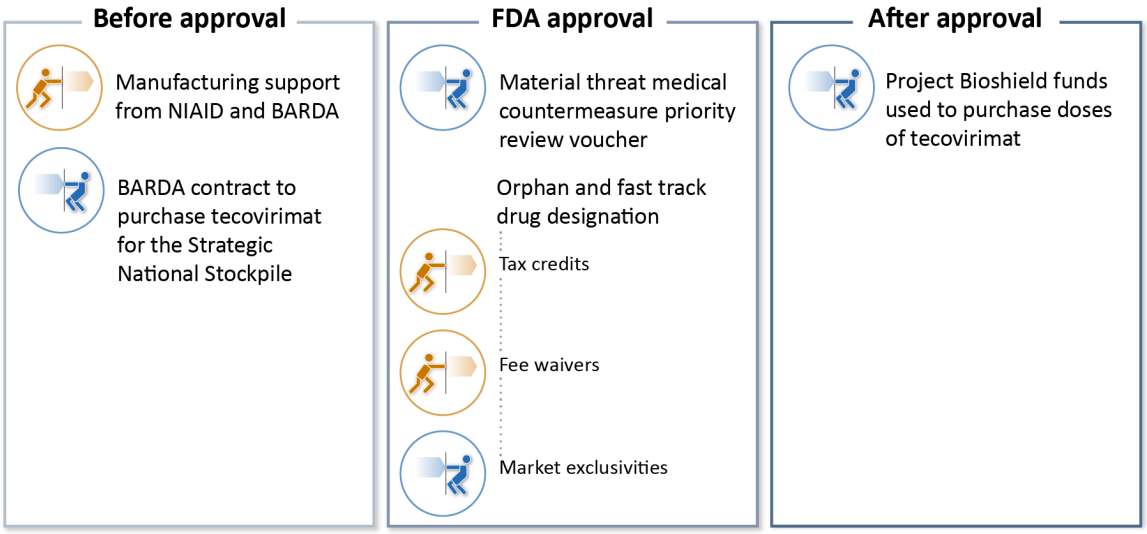
[48]The Strategic National Stockpile is a multibillion dollar federal inventory of medical countermeasures that can be used to respond to a broad range of emergencies.

[49]Fast track designation facilitates the development, and expedites the review, of drugs intended to treat serious conditions that demonstrate the potential to address unmet medical needs. 21 U.S.C. § 356(b) and (d). Fast track designation may include advantages such as more frequent interactions with the FDA review team and rolling review of the product application.

[50]FDA may award a priority review voucher to a sponsor of a medical countermeasure upon approval of the drug, provided certain statutory criteria are met. See 21 U.S.C. § 360bbb-4a. The drug sponsor can later redeem the voucher when submitting a future drug application to treat any disease or condition or can sell or transfer it to another drug sponsor. When redeemed, a voucher entitles the sponsor to priority review of their application, which generally means a 6-month review goal rather than a 10-month goal for standard review. The potential for additional revenue that comes from marketing a drug approximately 4 months earlier, or the proceeds that come from selling the voucher, could incentivize drug sponsors to develop medical countermeasures.

[51]Drugs granted orphan designation are those that are intended to prevent, diagnose, or treat rare diseases. A rare disease is one that affects fewer than 200,000 people in the United States or one that affects more people but for which there is no reasonable expectation of recovering the cost of development and marketing from U.S. sales. 21 U.S.C. § 360bb(a).

**Figure 7: Federal incentives used to support development of Tecovirimat to treat smallpox**




BARDA = Biomedical Advanced Research and Development Authority
FDA = U.S. Food and Drug Administration
NIAID = National Institute of Allergy and Infectious Diseases

Source: GAO analysis; GAO (icons). | GAO-23-105847

## 3.2 Scale and scope of incentives

Experts said that the scale and scope of incentive options can be tailored to address a variety of circumstances, including:

**Adjusting incentives according to development stages of drug candidates.** Experts noted that because various pandemic drug candidates will be at different stages of drug development, incentives would need to be tailored accordingly. Because there is less certainty that early-stage research and development will ultimately lead to a successful drug, push incentives' effect on lowering research and development costs makes them useful early in the drug development cycle. As a result, push funding, such as grants, contracts, and tax credits, can be effective in supporting early-stage development, including phase 1 clinical trials. On the other hand, pull funding, because it ensures a buyer for completed drugs, can be used to incentivize later-stage drug development, in phase 2 or phase 3 clinical trials. Pull incentives may include a commitment to purchase a specified quantity of a drug to maintain as part of a stockpile of medical countermeasures available for use during public health emergencies.

**Tailoring incentives for products with commercial value independent of pandemics.** Some drugs, such as antibiotics, can treat existing diseases and can better align private incentives with social needs because they can generate revenue absent a pandemic. Experts told us that public investment in incentives could be inversely related to the commercial value of developed products. That is, incentives can be smaller for products with higher commercial value, independent of pandemic use—for example, antiviral drugs

that can treat seasonal influenza as well as pandemic influenza.[52]

## 3.3 Incentives for addressing drug manufacturing capacity and supply chain concerns

Experts we spoke with identified economic incentives and other policies for both manufacturing capacity and supply chains that could enhance preparation for potential future pandemics.

**Cost-sharing agreements and contracts for manufacturing capacity**.

Government can assume some costs of building and maintaining drug manufacturing through cost-sharing agreements with manufacturers. Building manufacturing capacity in advance of a pandemic can reduce the marginal costs and increase return on investment for pandemic drugs.[53] Cost-sharing agreements have been used to support manufacturing capacity and other costs for antiviral drugs. For example, in 2013, CDC supported the development of remdesivir with a cost-sharing agreement for agency laboratory spaces, among other things. Cost-sharing agreements also shift some of the risk to drug manufacturers by ensuring that newly developed capacity is in fact useful and necessary. One expert said that where existing capacity is available, governments could award contracts to reserve that capacity with manufacturers. For example, during the COVID-19 pandemic, HHS used contracts to reserve existing capacity to produce products at a larger scale to aid the pandemic response.[54]

**Efforts to strengthen the supply chain.** Policies that enhance international cooperation can increase and strengthen manufacturing and supply chain resilience for pandemic drugs.[55] Such efforts could include economic cooperation tools such as multilateral and bilateral agreements that include commitments to keep trade flowing during crises—as well as measures to reduce trade barriers for critical supply chain products.[56] These types of agreements can give countries the confidence that investments in standby capacity will not be curtailed during crises, broadening the portfolio of available capacity countries can

[52]BARDA noted that a potential commercial market may not offer enough incentive. For example, the price of oseltamivir, an antiviral drug for the treatment of influenza, is so low that baloxavir, a brand name drug for the treatment of influenza, has not gained market share.

[53]We have previously reported that the investing in development and manufacturing capacity in preparation for future pandemics has the potential to reduce costs for drugs because investments undertaken at a more measured pace do not stretch scarce (and thus expensive) inputs and avoid the government having to pay premiums on those inputs. See GAO, *Vaccine Development: Capabilities and Challenges for Addressing Infectious Diseases*, GAO-22-104371 (Washington, D.C.: Nov. 16, 2021).

[54]An internal HHS review found that—for various reasons—a lack of regular manufacturing by either HHS or other manufacturers prevented the sites from developing the capability to rapidly produce countermeasures at a large scale as the program intended. For more information see GAO, *Public Health Preparedness: HHS Should Plan for Medical Countermeasure Development and Manufacturing Risks*, GAO-23-105713 (Washington, D.C.; Feb. 2, 2023).

[55]Several U.S. government efforts aim to strengthen supply chain resilience with international partners. See GAO, *Supply Chain Resilience: Agencies Are Taking Steps to Expand Diplomatic Engagement and Coordinate with International Partners*, GAO-23-105534 (Washington, D.C.: Feb. 2, 2023). Also see U.S. Department of Commerce, "Joint Statement on Cooperation on Global Supply Chains" (July 20, 2022), https://www.commerce.gov/news/press-releases/2022/07/joint-statement-cooperation-global-supply-chains.

[56]OECD, "Keys to Resilient Supply Chains: Policy Tools for Preparedness and Responsiveness," accessed May 23rd, 2023, https://www.oecd.org/trade/resilient-supply-chains/.

access. In contrast, strengthening domestic capacity in advance of a pandemic can help reduce supply chain risks if other countries are likely to institute export bans on certain key ingredients or final products during times of crisis.

## 3.4 Government incentives and support for additional policy goals

According to experts, depending on how incentives are structured, they can also target other desirable policy goals—including making antiviral drugs more accessible and promoting innovation.

### 3.4.1 Accessibility

Ensuring that antiviral drugs are accessible to everyone at low or no cost can help mitigate the spread of disease. One expert said that if the policy goal is to make antiviral drugs widely available, having a large supply of products is important. For example, purchase commitments can allow drugs to be available to everyone who needs them, while protecting the intellectual property for developers. In addition, some experts told us that high-income countries can subsidize products for low-income countries without the need to waive intellectual property rights on these products.

### 3.4.2 Innovation

Developing innovative technologies and processes is essential to broadening the supply of antiviral drugs and can offer additional benefits in other areas of health. For example, there is value to understanding how pandemic pathogens affect humans and to broadening basic scientific knowledge, an area of research in which the private sector is less likely to invest despite its potential value to both the private sector and society. Additionally, investment in drug discovery tools can help antiviral drug development, but can also aid the development of other drugs for existing commercial markets.

# 4 Pandemic Antiviral Drug Preparedness Strategy

To counter biological threats, including epidemics and pandemics, in October 2022 the White House issued the *National Biodefense Strategy and Implementation Plan*, which calls for, among other things, the development of two antiviral drugs focusing on outbreak-prone viral families that would be ready for domestic stockpiling within 5 years. Experts we spoke with agreed this was a positive step. They also described additional elements of planning and developing a strategy to guide the use of economic incentives to make drugs available for future pandemics. According to experts, key components of a plan for antiviral drug preparedness should include

- developing pandemic scenarios,
- developing multiple novel antiviral drugs through phase 1 clinical trials,
- fully developing some antiviral drugs for stockpiling,
- developing a range of antiviral drugs,
- developing broad-spectrum antiviral drugs,
- reviewing existing antiviral drugs, and
- designating a single entity for pandemic antiviral drug development.

## 4.1 Pandemic scenarios

Experts said developing plausible scenarios of pandemic pathogen outbreaks could allow for a systematic determination of the number of candidates and quantities of particular antiviral drugs across viral families that might be needed in advance of a pandemic. According to the WHO, pandemic scenarios are hypothetical yet plausible illustrations of the future and can serve as a tool for framing decision-making, identifying recommendations, and testing and refining strategy or policy options. Effective scenarios recognize the global nature of potential outbreaks, as recent scenarios from WHO demonstrated.[57]

The U.S. government has also conducted assessments of the criticality of drugs, vaccines, and other materials that can be used to respond to a broad range of emergency scenarios. For example, ASPR conducts an annual threat-based review of the contents of the Strategic National Stockpile to determine whether such contents are consistent with stockpiling recommendations. [58] According to ASPR officials, these reviews are used to develop plans for purchasing medical countermeasures, such as tecovirimat.

[57]In June 2021, the WHO commissioned a set of scenarios on the future of the COVID-19 pandemic and other infectious threats. This project engaged WHO officials and officials from WHO partner organizations from across the world on how the pandemic and other infectious threats might evolve in the future.

[58]See 42 U.S.C. § 247d-6b(a)(2). We previously reported that the Strategic National Stockpile contained most recommended medical countermeasure types but often not in the recommended quantities. HHS officials noted that gaps in quantities are due to budget constraints and acknowledged that these gaps present risks. See GAO, Public Health Preparedness: HHS Should Address Strategic National Stockpile Requirements and Inventory Risks, GAO-23-106210 (Washington, D.C.: Oct. 17, 2022).

Furthermore, CDC conducts scenario development for known biological threats, such as the SARS-CoV-2 virus. CDC and ASPR, among others, developed pandemic planning scenarios for the COVID-19 pandemic using mathematical modeling to help evaluate potential effects of community mitigation strategies.[59]

Experts we spoke to agreed that scenarios could inform decisions on how to prioritize research funding and incentives among pathogen families. Key factors could include transmissibility, variant diversity, human vulnerability, mortality rates, and potential economic damage. Scenarios could also be integrated with cost-benefit analyses that examine, for example, the likelihood of a pandemic and the potential damage to health and the economy. The likelihood and severity of damage to health and the economy could be weighed against the total cost of developing relevant drugs and incentivizing needed manufacturing capacity to produce them.

Cost-benefit analyses can also help decision-makers prioritize investment in the presence of limited resources. For example, pathogens predicted to cause milder illnesses would be less impactful and might not warrant a large investment relative to pathogens expected to cause severe illness. Further, scenarios could take into account the existing level of drug development for a given pathogen, including pathogen families for which no known antiviral drugs have reached phase 1 clinical trials (i.e., paramyxoviruses, picornaviruses, togaviruses, and bunyaviruses). The text box lists viral families with high pandemic potential.

**Viral families with high pandemic potential**

In December 2021, the National Institute of Allergy and Infectious Diseases (NIAID) produced the NIAID Pandemic Preparedness Plan, which focused predominantly on viruses that could cause epidemics or pandemics. NIAID identified viral families with high potential to cause a pandemic in the future, including paramyxoviruses (including the Nipah virus), bunyaviruses (including Rift Valley fever, which may cause encephalitis), togaviruses (including Chikungunya), filoviruses (including Ebola viruses and Marburg virus), picornaviruses (including enteroviruses and other cold-causing viruses), and flaviviruses (including the viruses that cause yellow fever, dengue and Zika). In addition, ASPR officials noted that influenza viruses are also among those most likely to cause a pandemic. Further, according to the Johns Hopkins Center for Health Security, there are several characteristics likely to be common to pathogens that constitute a global catastrophic risk such as a pandemic. Although most classes of microbes could evolve to cause a catastrophic risk, viruses—especially RNA viruses—are the most likely class of microorganisms to have this capacity.

Source: National Institute for Allergy and Infectious Disease, NIAID Pandemic Preparedness Plan, (Dec. 2021). The Characteristics of Pandemic Pathogens, Johns Hopkins Bloomberg School of Public Health, Center for Health Security, 2018. | GAO-23-105847

## 4.2 Developing multiple antiviral drugs through phase 1 clinical trials

Because antiviral drugs with potentially large social benefits mostly do not exist and because it is difficult to know which will be effective, experts agreed that a robust pipeline of early stage drug candidates may be needed in advance of a pandemic. BARDA officials said and experts agreed that

[59]For additional information on the methodology for these pandemic planning scenarios, see Centers for Disease Control and Prevention, "COVID-19 Pandemic Planning Scenarios," accessed July 10th, 2023, https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.

developing dozens of antiviral drugs through at least phase 1 clinical trials, in combination with a clear development pathway, may be feasible. Experts also agreed that this development done in combination with a clear pathway for further clinical trials and eventual FDA approval may also be feasible.

Further, experts agreed that taking a larger number of antiviral drug candidates through an interim level of development, such as phase 1 clinical trials, may be a lower cost option than taking fewer candidates through later stages of development. This approach would provide additional flexibility to respond to a broad range of potential pandemic pathogens. One industry expert also stated that process innovations to accelerate the clinical trial process, including standardized assays and common control groups, as well as the use of remote clinical trials and wearable devices to expedite collecting data from patients, can help early stage drug candidates get authorized or approved more quickly during a pandemic.

However, experts also concurred that developing an antiviral drug to an interim stage of development would leave uncertainty in manufacturing plans, specifically in workforce readiness and available manufacturing sites, and uncertainty as to which drug will be most effective against a particular virus.[60] Therefore, taking antiviral drug candidates through phase 1 clinical trials would not obviate the need for sufficient manufacturing capacity or the need for clinical efficacy trials when the virus emerges.

Further, experts said that a workforce with sufficient training and capability must be available to operate facilities.[61]

## 4.3 Fully developing some antiviral drugs for stockpiling

Experts also concurred that some antiviral drugs could be developed to completion or near completion. Therefore, these drugs would be more readily deployable in the event of an outbreak of pathogens with the most significant pandemic potential and the most serious consequences, as determined through scenario analysis. Such drugs could be stockpiled—such as through the Strategic National Stockpile—to enable an even faster response during outbreaks and provide lead time for manufacturing additional therapeutic responses. Alternatively, it may not be necessary to stockpile antiviral drugs for pathogens that are less likely to be transmissible or for pathogens that are likely to affect a smaller subset of the population, such as those with preexisting conditions. Rather, sufficient quantities of such drugs might be produced with existing manufacturing capacity when needed.

## 4.4 Developing a wide range of antiviral drug candidates

Experts told us that having a wide range of antiviral drug candidates that use different mechanisms of action across a larger number of viral families could provide greater flexibility to respond to a wider range of

[60] GAO-23-105713.

[61] We have reported on the importance of developing and maintaining modern, flexible, rapid, and robust vaccine development and manufacturing capabilities. These capabilities would allow for better response to endemic levels of infectious disease as well as better preparation for potential future pandemics. See GAO-22-104371.

pathogens and address the uncertainty associated with the pathogen that may cause the next pandemic. NIAID officials said that it can be challenging to predict whether a given antiviral drug will be effective against a future pandemic-causing virus. Therefore, having a larger number of antiviral drugs utilizing different mechanisms of action available to respond to pandemics could enhance overall pandemic preparedness. This may also allow for a more flexible response to pandemic pathogens and prove beneficial should a pandemic virus develop antiviral drug resistance.[62]

Importantly, while antiviral drugs may demonstrate efficacy during testing against target pathogens, the effectiveness may be limited in an actual outbreak, which according to experts, points to the benefit of having multiple antiviral drug candidates.

## 4.5 Development of broad-spectrum versus

Experts we spoke with said that encouraging the development of broad-spectrum antiviral drugs—effective against a range of viruses within a family or across virus families—could reduce the effect of uncertainty about the pathogen that will cause the next pandemic. According to ASPR officials, because future pandemics are likely to be caused by a virus that is related to an already known pathogen, a focus on antiviral drugs that are effective against families of viruses is preferable. Experts agreed that developing these broad-spectrum antiviral drugs in advance could also allow companies to establish manufacturing capacity in advance and maintain that capacity to increase the likelihood that the antiviral drugs could be produced in quantities sufficient to respond to potential future pandemics. They also agreed that although broad-spectrum drugs can be more difficult to develop and may have less effectiveness than a more targeted drug, these drugs could serve as a first line of defense against a future viral pandemic of unknown origin.

## 4.6 Reviewing existing antiviral drugs

One expert we spoke to cautioned against relying on existing drugs in response to a pandemic but added that they could be tested quickly for efficacy and used as an initial response to a pandemic**.** Clinical efficacy trials would still be necessary and could benefit from being carried out rapidly at the onset of an outbreak, using the technologies described above—artificial intelligence, high throughput screening, and organ chips. For example, in 2021, researchers determined that human lung airway chips could be used to model human lung responses to viral infection to identify existing approved drugs that have the potential to be repurposed for treating viral pandemics caused by influenza or SARS-CoV-2 viruses.[63]

Using existing antiviral drugs to address the "first wave" of cases may allow more time for the development of novel antiviral drugs that are designed to treat against the specific

[62]See also Aeron Hurt, "Antiviral Therapy for the Next Influenza Pandemic," *Tropical Medicine and Infectious Disease*, vol. 4, no. 2 (2019):67.

[63]Longlong Si, Haiqing Bai, et al., "A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics," *Nature Biomedical Engineering*, vol. 5, no. 8 (2021): 815-829.

pathogen, according to one expert we spoke to. The expert stated that existing or repurposed drugs could serve as a starting point so that they are better positioned to later develop a more effective antiviral drug. See the text box for a description of the repurposing of an existing drug, remdesivir, to treat COVID-19.

**Redirecting Broad-Spectrum Antiviral Drugs: Remdesivir Case Study**

In October 2020, remdesivir became the first treatment approved by the Food and Drug Administration (FDA) for treating COVID-19. Remdesivir is an antiviral drug that was originally developed for treating viral hepatitis and respiratory syncytial virus infection but did not receive approval.

In 2013, the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) began supporting and conducting preclinical research that helped to demonstrate remdesivir's broad spectrum properties against coronaviruses, such as Middle East respiratory syndrome coronavirus (MERS-CoV), as well as Ebola virus. Because remdesivir had already been through phase 2 and 3 clinical trials (for Ebola) before the COVID-19 pandemic and because it had been shown to be effective against MERS-CoV in pre-clinical models, efforts to use remdesivir against SARS-CoV-2 infection in patients started shortly after the pandemic began. In February 2020, NIH funded clinical trials at the onset of the COVID-19 pandemic. On May 1, 2020, three months after the COVID-19 public health emergency declaration, FDA issued an emergency use authorization for remdesivir for the treatment of hospitalized patients with severe COVID-19 disease. FDA issued the authorization based in part on NIH-funded COVID-19 clinical trial results, which suggested that remdesivir shortens recovery time in hospitalized patients with severe COVID-19.

Source: GAO, Biomedical Research: Information on Federal Contributions to Remdesivir, GAO-21-272 (Washington, D.C.: Mar. 31, 2021). | GAO-23-105847

## 4.7 Designating a single entity for pandemic antiviral drug development

Experts from our panel said that there may be benefits associated with making a single entity within HHS accountable for the development and manufacturing of pandemic antiviral drugs to address potential future pandemic threats.[64] HHS, through its entities including BARDA, NCATS, and NIAID, has created programs to develop pandemic antiviral drugs, though experts said that it could be beneficial to give one entity overall responsibility for shepherding new pandemic antiviral drugs from initial research and development to manufacturing. Experts indicated that this single entity would promote consistent, accountable leadership and focus on pandemic antiviral drug development and availability.

According to experts, antiviral drug candidates do not automatically move through the development pipeline from early stage research at NIH, to development at BARDA, and on to FDA for approval. According to HHS officials, this is in part because NIH has the authority to develop drugs for a wider range of pathogens that could cause future pandemics, but BARDA is limited to chemical, radiological, nuclear, and biological threats. Moreover, NIH officials told us that a pathogen's inclusion on the agency's list of high-risk pathogens does not automatically result in additional efforts to develop drugs for that pathogen.

[64]The Consolidated Appropriations Act, 2023 included certain provisions related to pandemic preparedness, such as the establishment of the Office of Pandemic Preparedness and Response Policy within the Executive Office of the President. See Pub. L. No. 117-328, § 2104, 136 Stat. 4459, 5715 (2022).

Experts from our panel said the single entity responsible for pandemic antiviral drugs could be an existing entity within HHS, such as BARDA, or a new entity. According to ASPR, BARDA is positioned to undertake this role because of existing coordination with NIH in certain areas, such as on treatments for pandemic influenza. They added that BARDA would need additional funding and authority to address additional pandemic pathogens. Experts said that the entity could be charged with ensuring that pandemic drug development would be carried out. This could include the development of some pandemic antiviral drugs to an interim stage of completion or through FDA approval and stockpiling.[65]

[65]Under 21 U.S.C. § 360bbb-3b, the Strategic National Stockpile may purchase products that have not been authorized or approved by FDA, provided those products are held and not distributed for use until they are authorized or approved.

# 5 Policy Options

A future pandemic is highly likely, and market failures and other challenges in pandemic antiviral drug development and manufacturing make it unlikely that market forces alone will support the availability of socially beneficial antiviral drugs in advance. There are currently few existing antiviral drugs for viruses with pandemic potential, and for some viral families there are no antiviral drugs even in phase 1 clinical trials. During the COVID-19 pandemic, antiviral drugs for SARS-CoV-2 were not available for about 4 months for hospitalized patients and nearly two years for an antiviral that could be taken orally for outpatient treatment. Policymakers could consider a number of options to achieve policy objectives through investments in pandemic antiviral drugs to improve overall health and economic outcomes when the next pandemic occurs. However, it is important to note that the presence of a market failure does not automatically imply that government intervention will be effective. Options for addressing market failures should strategically weigh the potential costs, benefits, and unintended consequences of public action, even in cases where there is broad consensus on the presence of market failure.

A strategy could guide policymakers in the use of incentives to develop multiple antiviral drugs aimed at the riskiest pathogens and to spur new drug development technologies. Experts stressed that, to enable the implementation of the strategy, one entity within HHS could lead the effort and be accountable for strategic investments in pandemic antiviral drug development and manufacturing. According to the experts, when multiple entities share fragmented responsibilities, no entity is accountable for the ultimate success of the effort, which could limit preparedness efforts in the face of uncertain but highly likely pandemic risks.

Further, such a strategy could take into account the economic and other challenges that, according to agency officials and experts, limit sustained investment and research in the development of antiviral drugs for pandemic pathogens. According to the White House, the administration's recently released *National Biodefense Strategy and Implementation Plan* aims to end unpredictable cycles of pandemic funding. Experts said that without consistent funding and additional flexibility to develop antiviral drug candidates, the U.S. government may have few antiviral drugs readily available to combat the next pandemic pathogen.

On the basis of expert input, GAO identified three key components that would facilitate the creation of antiviral drugs in preparation for future pandemics:

1. A strategy to focus on developing diverse therapeutic antiviral drugs to respond to pandemics caused by the most dangerous pathogens,
2. An entity with the authority and accountability for implementing the strategy, and
3. Economic incentives to mitigate economic obstacles to the development and availability of pandemic antiviral drugs.

Table 4 describes opportunities and challenges related to these various policy options for consideration by policymakers, which may include Congress, federal agency officials, state and local governments, academic and research institutions, industry, and international organizations. Policymakers would need to consider how these potential actions would need to be aligned with existing federal programs and initiatives, including the *National Biodefense Strategy and Implementation Plan* and the Office of Pandemic Preparedness and Response Policy in the White House.

**Table 4: Policy options, opportunities, and considerations to facilitate the development of antiviral drugs to prepare for future pandemics**

| Policy option | Opportunities | Considerations |
|---|---|---|
| **Create a strategy to focus on developing diverse antiviral drugs to respond to pandemics caused by the most dangerous pathogens**<br><br>Policymakers could ensure focus on pathogens and pathogen families that are most likely to cause severe future pandemics, such as flaviviruses and bunyaviruses, with an emphasis on pathogen families with no current drug candidates in clinical trials.<br><br>Policymakers could use pandemic scenarios, in cooperation with relevant stakeholders and international entities, to determine which and how many antiviral drugs to develop, the stage to which those antiviral drugs should be developed, the quantities and manufacturing capacity that may be needed to address potential future pandemic threats, and the level of funding needed to achieve different levels of preparedness. | • Designing hypothetical pandemic scenarios could help identify the relative likelihoods that an outbreak could quickly become severe and widespread, indicating which antiviral drugs may need to be stockpiled—for example through the Strategic National Stockpile--and which only need to be developed to phase 1 clinical trials.<br>• Developing drug candidates through phase 1 clinical trials would provide information on the initial safety profile and side effects of different doses in advance of potential pandemics.<br>• Developing scenarios in cooperation with international entities, such as the WHO, can help coordinate global pandemic preparedness.<br>• Focusing attention on viral families with no drug candidates in clinical trials could spur research and development.<br>• Pandemic scenarios could provide a range of possible effects for any given pathogen (e.g., more severe vs. less severe outbreaks). | • Not every possible pandemic scenario can be considered, and pandemic pathogens may not appear on known lists of pathogens that may cause future pandemics.<br>• It is difficult to predict how a novel pathogen may travel across populations. Therefore, assessing the stage to which each drug candidate should be developed and how much manufacturing might be needed may be difficult.<br>• Developing multiple pandemic antiviral drug candidates increases the cost of pandemic preparation and may require additional appropriations.<br>• Other drugs for high-risk pathogens not the focus this report, such as host targeted therapeutics, could supplement investment in antiviral drugs.<br>• Policymakers, including Congress, may need to establish the level of preparedness they want to achieve with respect to the overall number of antiviral drugs, drug candidates, and doses to be available. |

| Policy option | Opportunities | Considerations |
|---|---|---|
| For example, policymakers could design pandemic scenarios that included issues such as the potential range of morbidity or mortality and virulence of a pathogen, potential economic effects, and the current state of drug development. This would help to determine if an outbreak would be likely to impact a large portion of the population or a more narrow set of individuals, such as the elderly or those with compromised immune systems.<br>Policymakers could also establish a goal of producing multiple pandemic antiviral drugs to address high risk pathogens and pathogen families based upon these scenarios. | • Determining antiviral drug manufacturing and supply chain capacity and operational readiness in coordination with international partners, and routinely re-assessing it, can help to identify gaps including assessing which drugs can be stockpiled or may need to be manufactured quickly during an outbreak.<br>• New drug development technologies could aid in identifying multiple antiviral drugs utilizing different mechanisms of action and aimed at different viral families to maximize the chance that a particular pandemic pathogen could be successfully treated. | • An effective strategy may require the expertise of antiviral drug researchers, industry, and other stakeholders.<br>• A strategy for developing antiviral drugs for pandemics may need to also reflect or incorporate additional priorities for antiviral drug development, including other biodefense related concerns. |
| **Assign a new or existing entity the authority to lead, implement, and be accountable for identifying and developing antiviral drugs for pathogens or pathogen families of greatest risk**<br>Policymakers could ensure that this entity has authority and accountability for making decisions and allocating resources to implement a strategy for addressing pathogens and pathogen families, informed by pandemic scenarios and the risks they present. | • A single centralized entity could direct strategic investments for pandemics, increase communication across federal agencies and with drug developers, and facilitate greater accountability for a more effective allocation of resources and a better response to the spectrum of pandemic threats.<br>• Having one entity explicitly accountable for pandemic preparedness and response can help effectively mitigate pandemic risks and help enhance government efforts to deal with uncertain but likely pandemic risks. | • Authorities among the entities within HHS vary, so designating an entity with responsibility and authority may require new directives or legislation.<br>• Any entity with such authority for pandemic antiviral drugs would need to coordinate or be aligned with related efforts, such as the development of vaccines, diagnostics, and surveillance, in order to be effective. |

| Policy option | Opportunities | Considerations |
|---|---|---|
| **Implement economic incentives to develop antiviral drug candidates and spur new drug-development technologies**<br><br>Policymakers could use various push and pull economic incentives to encourage the development of pandemic antiviral drugs, informed by the economic costs of scenarios, scientific opportunities, and pathogen priorities. They could also consider other policy priorities, such as drug accessibility.<br><br>Policymakers could use various push and pull incentives to further spur the development of technologies such as organ chips, high throughput drug screening methods and technologies to accelerate clinical trials.<br><br>Policymakers could use push and pull economic incentives to stockpile certain drugs and active pharmaceutical ingredients in advance of a pandemic, as well as ensuring sufficient manufacturing capacity to be used, expanded, created, or repurposed during a pandemic.<br><br>Policymakers could consider appropriating predictable and consistent funding to a program and entity in charge, to allow for strategic investments and encourage private participation in the development of drugs for future pandemics. Consistency and predictability in funding can be valuable features of funding for pandemic preparedness for any level of funding. | • Economic incentives could address the challenges related to critical market failures that have limited investment in pandemic antiviral drugs. Through such actions, economic and societal costs from viral pandemics could be meaningfully reduced.<br><br>• Manufacturing capacity for pandemic antiviral drugs may be able to be used to manufacture similar antiviral drugs with an existing commercial market.<br><br>• New drug development technologies spurred from investment in pandemic antiviral drugs may allow for the treatment of nonpandemic infectious diseases, especially for those pathogens in the same family as those targeted for antiviral development.<br><br>• Incentives could be coordinated internationally, based on needed manufacturing capacity and international supply chains. International coordination may improve efficiency and manage costs because different countries specialize in different production, and thus expand the potential capacity during a crisis. | • Periodic updates to evaluations of pandemic risks would be needed to guide how economic incentives for new antivirals, and drug development technologies could be deployed, and the extent of investment needed, as new pandemic pathogens arise.<br><br>• Evidence on the full range of potential pandemic costs may be unavailable or insufficient to make precise determinations of the level of investment needed to achieve certain levels of preparedness.<br><br>• Manufacturing capacity is expensive to establish and maintain. Technologies used for manufacturing may not be relevant or useful for pathogens that cause pandemics (i.e. manufacturing capacity for flu antiviral drugs may not be useful for coronavirus antiviral drugs).<br><br>• Policymakers face a range of important and competing priorities for funding investments across programs and areas of the economy.<br><br>• International coordination on supply chain and manufacturing could take time to establish, and international supply chains could increase risks in the event countries institute export bans during a crisis. |

Source: GAO. | GAO-23-105847

# 6 Agency and Expert Comments

We provided a draft of this report to the Department of Health and Human Services (HHS) with a request for technical comments. HHS provided technical comments, which we incorporated into the report where appropriate.

We also provided our draft to the experts for their review, consistent with previous technology assessment methodologies. We incorporated their comments where appropriate.

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We are sending copies of this report to the appropriate congressional committees, relevant federal agencies, 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 us at 202-512-6888 or WrightC@gao.gov or at HoffmanME@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 contributions to this report are listed in appendix III.

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Applied Research and Methods

## *List of Committees*

**The Honorable Patty Murray**
Chair
**The Honorable Susan Collins**
Vice Chair
Committee on Appropriations
United States Senate

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Chairman
**The Honorable Mike Crapo**
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**The Honorable Bill Cassidy**
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# Appendix I: Scope and Methodology

## Scope and Methodology

This report discusses:

1. The economic effects of pandemics and types of antiviral drugs and related technologies

2. Factors affecting market incentives for pandemic antiviral development and manufacturing

3. Mechanisms to incentivize antiviral drug development and manufacturing

4. Strategies to treat viral families at high risk of causing pandemics

5. Potential policy options

To address our first objective, we described technologies and process innovations that can make antiviral drugs less costly and safer. We also described how agencies in the Department of Health and Human Services (HHS) are supporting antiviral drug development. For our second objective, we described market failures and other economic challenges associated with drug development. For our third objective, we described potential economic mechanisms for incentivizing antiviral drug development. For our fourth objective, we noted current plans to counter future pandemics and described additional elements of planning and strategy development to guide the use of economic incentives to make drugs available for future pandemics. For our fifth objective, we identified three policy options that would facilitate the creation for antiviral drugs in preparation for future pandemics.

### Limitations to scope

We focused this technology assessment on antiviral drugs for pandemic pathogens and some of the existing and emerging technologies that could be used for drug development in advance of a pandemic. We did not assess fungal, parasitic, or other pathogens because of their limited ability to cause pandemics. We also did not assess foodborne pathogens or outbreaks. Our discussion of economic challenges included market failures for pandemic antivirals as well as types of economic incentives for drug research and development.

### Interviews

We interviewed federal officials, industry organizations, economists, and experts on issues related to our engagement objectives such as antiviral drug types and technologies, the economics of antiviral drug development, and strategies for addressing antiviral drug development. For our first objective we discussed the human and economic costs of pandemics, types of antiviral drugs to treat viral pathogens, and federal efforts to support their development. For our second objective, we discussed market failures and other market factors that inhibit investment in pandemic antiviral drugs as well as market failures in manufacturing capacity to produce them. For our third objective we discussed types of economic incentives for drug research and development and the use of economic incentives to develop antiviral drugs to different stages of completion. For our fourth objective, we discussed developing scenarios for pandemic pathogen outbreaks to inform the development of antiviral drugs for potential future pandemics.

## Expert meeting

To address all of our objectives and identify economic incentives for the development and manufacturing of antiviral drugs for potential future pandemics, we held a virtual expert meeting on October 11, 2022, and on October 14, 2022. This meeting of experts was convened with the assistance of the National Academies of Sciences, Engineering, and Medicine (National Academies) to better ensure that participants could discuss incentives to promote investment in pandemic antiviral drugs. However, all final decisions regarding expert participation were made by GAO. The panels were divided into four sessions and moderated by five representatives from GAO. The topics of each session were as follows: (1) necessary components of preparedness with regard to antiviral drugs for potential pandemics, (2) federal government efforts to achieve preparedness, (3) economic incentives to enhance the development and availability of antiviral drugs for pandemic preparation, and (4) potential policy options.

## Participant selection

To prepare for the expert meeting, GAO contracted with the National Academies to assist in selecting participants. Meeting experts were selected if they had expertise in antiviral drug development, pandemic antiviral markets, or economic incentives for pharmaceutical development and manufacturing. We provided the National Academies with descriptions of the expertise needed by meeting participants. We sought representation of experts from the following fields: economics, biology, virology, health security policy, pharmacology, biotechnology, pharmaceutical manufacturing, and former government officials, including former Biomedical Advanced Research and Development Authority officials. From this information, the National Academies provided a list of experts to potentially participate in the expert meeting. We reviewed the list and provided an additional list of experts based on expert availability for the sessions. A total of 16 experts participated in various sessions.

## Independence of participants

We met with the National Academies to help ensure balance and to help us assess potential conflicts of interest for meeting participants, with GAO making final determinations regarding potential conflicts of interest. To exercise due diligence and to understand meeting participants' potential conflicts of interest, we asked all meeting participants to sign a form that asked participants (1) whether their immediate family had any investments or other assets that could be affected, in a direct and predictable way, by a decision or action based on the information or opinions they would provide to GAO; (2) whether they or their spouse received any income or hold any organizational positions that could be affected, in a direct and predictable way, by the information or opinions they could provide GAO; and (3) whether there were any other circumstances, not addressed in the two previous questions, that could be reasonably viewed by others as affecting participants' point of view on the topics to be discussed. GAO received signed responses from all meeting participants where they identified any affiliations that could affect their independence. We determined that these experts' relationships did not result in any inappropriate biases in our reporting. Expert meeting participants were informed that GAO would not directly identify individuals or their affiliations in association

with specific comments (without their permission), and this product does not do so.

### Creation of a Briefing Book

To develop common background material for participants we prepared a briefing book to provide information to stimulate discussion among the broad array of experts representing varied perspectives. Additionally, it provided background material on the purpose of the technology assessment, why GAO was convening the expert meeting, and what the meeting would examine.

### Participant follow-up

To better understand or develop points raised by participants in the meeting, we reviewed meeting transcripts and interacted with participants after the meeting, as needed. Before publication, we offered participants a draft of the report for their review and comment. On that basis, 9 of our 16 experts were able to review the draft. Three of the 16 participants provided comments on the draft report, which we incorporated as appropriate.

### Potential policy options

Based on information from discussions with academic, industry, and government officials, as well as literature reviews and related analyses, we developed a list of potential policy options. Policy options are not formal recommendations for federal agencies or matters for congressional consideration, but they are intended to represent a set of alternatives or a menu of options that policymakers, such as legislative bodies, government agencies, or other groups, could consider taking.

To develop our policy options, we compiled a list of thirteen possible options. Based on interviews with experts and our expert meeting, we refined and revised this list to compile our final list of three policy options.

### Quality assurance statement

We conducted our work from February 2022 to September 2023 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 technology assessment.

## Appendix II: Expert Meeting Participation List

We collaborated with the National Academies of Science, Engineering, and Medicine to convene a meeting of experts over 2 days to inform our work on this technology assessment. The meeting was held virtually on October 11 and 14, 2022. Experts who participated in this meeting are listed below. We corresponded with experts for additional assistance throughout our work and provided our draft report to the experts for their technical review, consistent with previous technology assessment methodologies.

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