Documents for the Record

02.01.23 E&C Oversight Hearing

"Challenges and Opportunities to Investigating the Origins of Pandemics and Other Biological Events"

1. Griffith
    a. Final GAO Report on Pandemic Origins
    b. GAO Report on Public Health Preparedness Recommendations
    c. HHS OIG EcoHealth Report
    d. Johns Hopkins Report on Biological Attribution

GAO

United States Government Accountability Office

Science, Technology Assessment, and Analytics

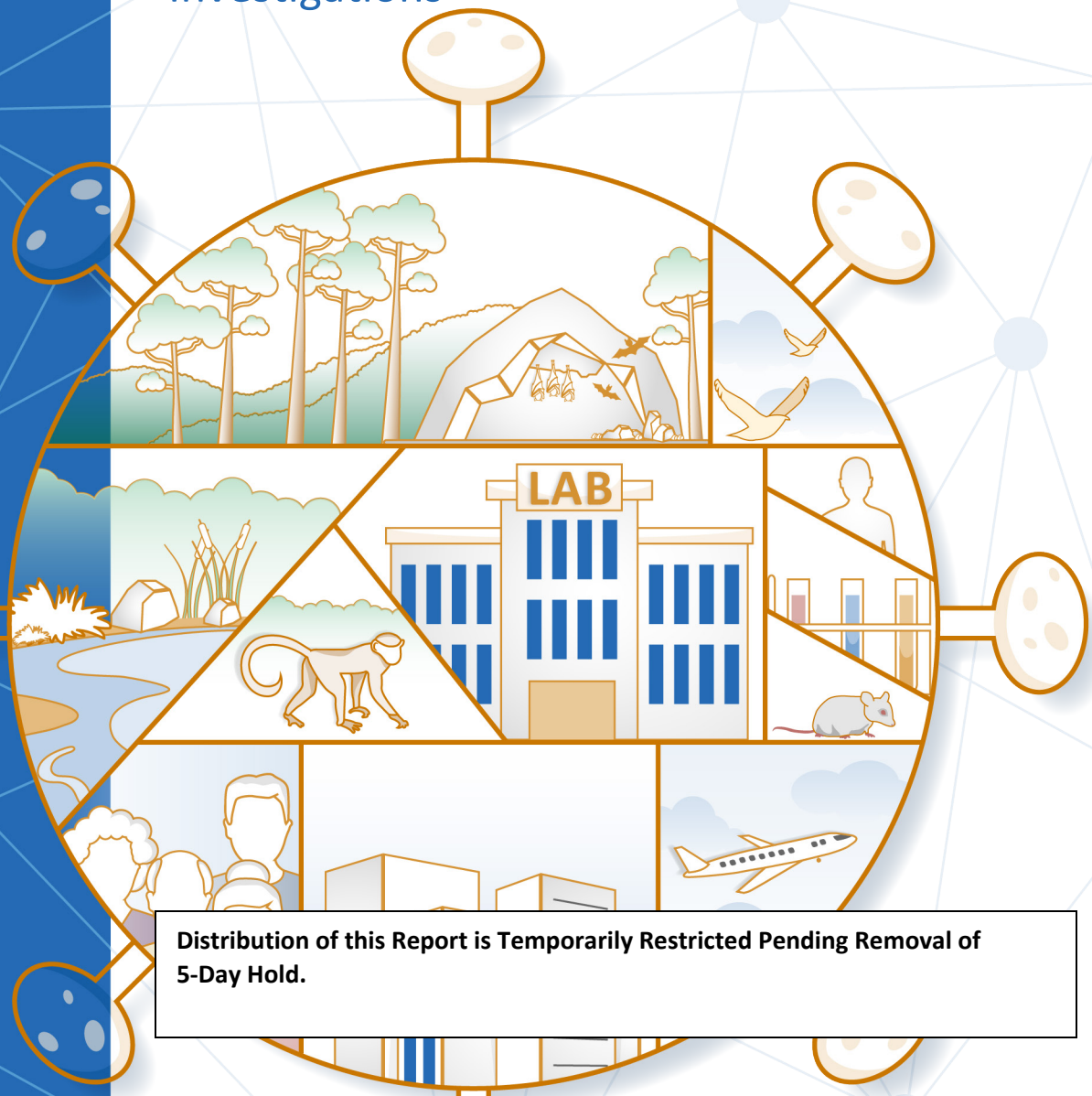
Report to Congressional Requesters

January 2023

TECHNOLOGY ASSESSMENT

Pandemic Origins

Technologies and Challenges for Biological Investigations



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The cover image displays examples of possible pandemic origin scenarios. These scenarios include natural origin—such as the accidental infection of one or more individuals by a pathogen transmitted from animals, including via insects or other sources such as the environment. Scenarios also include laboratory origin that begins with either the infection of individuals by a pathogen in a laboratory setting, or infections outside the laboratory caused by an accidental or intentional release of the pathogen from a laboratory.

Cover source: GAO. | GAO-23-105406

Highlights of GAO-23-105406, a report to congressional requesters

January 2023

TECHNOLOGY ASSESSMENT

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Technologies and Challenges for Biological Investigations

Why GAO did this study

Pandemics are global disease outbreaks that can greatly increase morbidity and mortality and cause significant economic and social disruptions. According to the scientific literature, most pandemics where the origin is known were caused by the natural transmission of a virus through animal-to-human contact; however, there is potential for a pandemic to originate from laboratory research.

GAO was asked to conduct a technology assessment on pandemic origins. This report describes: (1) key technologies available for pandemic origin investigations, (2) strengths and limitations of these tools and how researchers use them to investigate pandemic origins, and (3) cross-cutting challenges researchers face in trying to determine a pandemic's origin.

GAO reviewed peer-reviewed scientific literature and other documents, including reports from the Centers for Disease Control and Prevention, Office of the Director of National Intelligence, the Johns Hopkins Center for Health Security, World Health Organization, and select national laboratories; interviewed government, industry, and academic representatives; and convened a meeting of 27 experts in March 2022 with assistance from the National Academies of Sciences, Engineering, and Medicine.

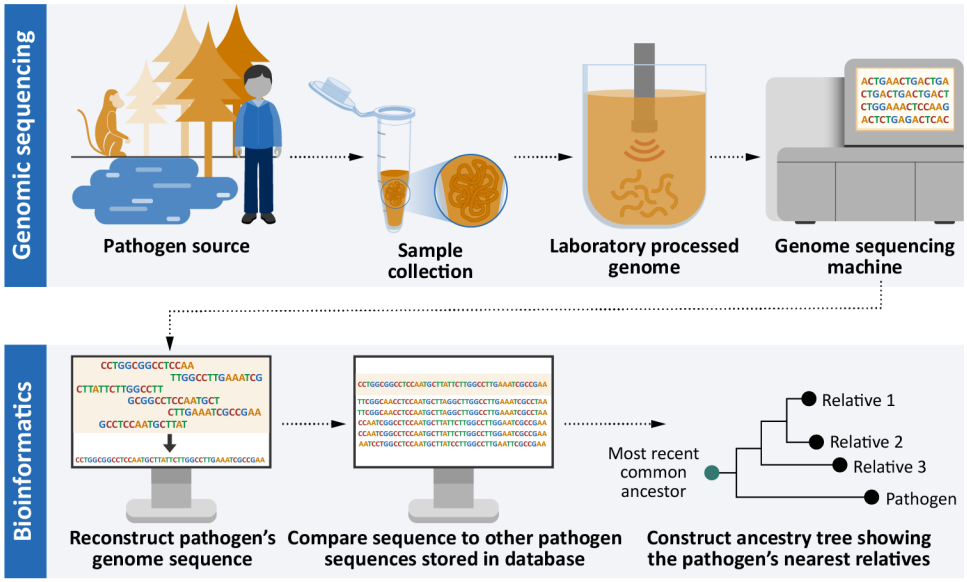
GAO is identifying policy options in this report.

View GAO-23-105406. For more information, contact Karen L. Howard at (202) 512-6888, howardk@gao.gov.

What GAO found

Determining the likely origin of pandemics is challenging. Researchers may use several technologies to investigate a pandemic's origin. For example, researchers use technologies such as genomic sequencing, bioinformatics analysis, and genetic databases to generate, analyze, and compare a pathogen's genetic makeup against that of other pathogens. A key limitation of these technologies is that some laboratory-based genetic modifications may be indistinguishable from natural variations. Access to samples is critical for conducting genetic sequence analysis, which allows researchers to generate and analyze the data needed to support the likely origin of a pandemic.

Examples of technologies for pandemic origin investigations



Source: GAO. | GAO-23-105406

Researchers also use technologies such as serology (i.e., blood analysis) and epidemiological surveillance—tracking a disease as it moves through a population—to monitor pathogen infection and disease occurrence in human and animal populations. The resulting data can support pandemic origin investigations. However, for these technologies to be effective in determining a pandemic's likely origin, investigators need access to samples and data from infected or exposed individuals from early in an outbreak to reliably trace the disease back to the first human infection(s). Further, researchers may conduct laboratory-based pathogen studies to generate data to support known natural patterns or unusual patterns of spread indicative of a possible laboratory-related origin. However, some pathogens cannot be easily cultured in a laboratory setting, and some pathogens may require enhanced biosafety-level facilities.

However, experts told GAO that technologies are not the limiting factor for determining the likely origin of a pandemic. GAO identified three cross-cutting challenges that hinder pandemic origin investigations. These include a lack of sufficient access to samples and genetic sequence data; a lack of standardized processes for submitting, accessing, and using genetic sequence data stored in databases around the world; and a lack of a sufficient and skilled interdisciplinary workforce.

GAO identified five policy options that may help address the cross-cutting challenges. These policy options represent possible actions that policymakers—who may include Congress, federal agencies, state and local governments, academia, industry, and international organizations—could consider taking. See below for a summary of the policy options and relevant opportunities and considerations.

Policy Options to Address Three Cross-Cutting Challenges in Pandemic Origin Investigations

Policy Option	Opportunities	Considerations
Establish multilateral agreements for accessing and sharing samples and genetic sequence data (report p. 21) Federal policymakers and others could encourage international preparedness in advance of future outbreaks by establishing multilateral agreements for accessing and sharing samples and genetic sequence data.	• Ensuring timely access to genetic information and samples in the critical beginning stages of a pandemic as well as throughout an origin investigation may help in the determination of a pandemic's origin. • Establishing standing agreements between nations before a pandemic occurs could assist in the determination of a pandemic's origin.	• Countries may be unwilling to participate in multilateral, international agreements because of concerns related to national sovereignty, among other reasons. • Identifying an appropriate responsible entity to determine and monitor whether countries are following agreed-upon standard processes may be time consuming and challenging.
Develop standardized processes for genetic sequence database use (report p. 22) Federal policymakers and others could empower or establish a working group to develop standardized processes for database use to support pandemic origin investigations.	• Developing standardized processes for database use could help ensure consistency of submitted data and metadata across multiple databases, improve researchers' access, and help researchers comprehensively compare genetic sequences. • Implementing leading practices for genetic data integrity and associated metadata could help improve the quality of data in genetic sequence databases.	• Standardized processes may be difficult to develop as there are risk-benefit trade-offs. For example, access to certain novel pathogen sequences should be limited to trusted and credentialed individuals with a need to access those sequences. • It may be challenging for multiple stakeholders to agree on what data are important.
Improve current, or develop new, genetic sequence database tools (report p. 23) Policymakers could encourage the improvement of current, or development of new, genetic sequence database tools.	• Improved or new database interfaces could streamline researchers' data submission, access, and use as well as improve data quality. • Improved or new database interfaces could help address the projected future growth in genetic sequence data.	• Building new, or retooling current, database interfaces could be time- and labor-intensive. • It may be challenging for groups of users to agree on what database interface features are important.
Encourage the development, retention, and growth of a workforce with the critical skills needed for pandemic origin investigations (report p. 24) Policymakers could encourage mechanisms to provide training, workforce development, and capacity-building, including in areas considered hot spots of emerging infectious disease.	• Encouraging development of expertise in geographic areas where novel pathogens are likely to emerge could increase the overall global supply of skilled workers and help to ensure the workforce is not concentrated in any geographic region. • A trained workforce skilled in origin investigations could contribute to other areas such as public health, or other types of related activities.	• Pandemic origin investigations tend to be episodic. As a result, it may be difficult to adequately plan for and consistently fund staffing in science fields related to pandemic origin investigations. • Researchers may experience unwanted attention or pressure because of their involvement in pandemic origin investigations and leave the field or refuse to participate.
Augment or develop a national strategy to better coordinate and collaborate domestically and internationally on pandemic origin investigations (report p. 25) Federal policymakers could better coordinate and collaborate with domestic and international partners by augmenting or developing a national strategy for pandemic origin investigations. This could be a standalone strategy or a component of existing strategies such as the National Biodefense Strategy.	• A national strategy could help address the challenges that hinder pandemic origin investigations. • Federal coordination and collaboration leadership, guided by a national strategy, could increase preparedness for future pandemic origin investigations. • Understanding pandemic origins could help mitigate health and economic costs associated with pandemics by, for example, facilitating surveillance that could identify future pandemics more quickly.	• Allocating resources and defining how federal agencies and others will collaborate may be challenging because of the number and types of entities with relevant expertise. • During nonpandemic periods, other priorities and needs may arise and make it challenging to provide sustained resources and support needed for maintaining a national strategy.

Source: GAO. | GAO-23-105406

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Abbreviations

API	application programming interface
CDC	Centers for Disease Control and Prevention
MERS	Middle East respiratory syndrome
MERS-CoV	MERS coronavirus
SARS	severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus

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January 27, 2023

Congressional Requesters

Pandemics and epidemics—such as plague, cholera, influenza, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19—have afflicted humanity throughout history, causing millions of deaths and costing trillions of dollars.[1] For example, prior to a successful vaccination campaign that eradicated smallpox in 1980, the disease killed approximately 300 million people globally between 1900 and 1980.[2]

The COVID-19 pandemic has highlighted how infectious diseases continue to have a devastating impact. As of the week ending January 7, 2023, the U.S. had about 1,090,000 reported deaths attributed to COVID-19.[3] A recent assessment estimated the human and economic cost of the COVID-19 pandemic to the U.S. totaled more than $10 trillion.[4]

Given the magnitude of the health and economic costs of pandemics, policymakers—which include Congress, federal agencies, state and local governments, academic and research institutions, industry, and international organizations—have a need to better understand how and where they originate.[5] This understanding could help inform preparation and response to future epidemics and pandemics. However, determining the origin of a pathogen—a bacterium, virus, or other microorganism that can cause disease—requires evidence that may, in some cases, take decades of research to acquire. The accumulated data from these investigations may lay the foundation for future pandemic origin-tracing. For example, it took approximately 13 years to determine the origin of the SARS-associated coronavirus (SARS-CoV) pathogen that

[1]The Centers for Disease Control and Prevention (CDC) describes a pandemic as an epidemic that has spread over several countries or continents; an epidemic as an increase in the number of cases of a disease above what is normally expected in an area; and an outbreak as an epidemic, but in a more limited geographic area. However, these terms are not always consistently used for every disease. For example, while some researchers describe MERS as a pandemic, others describe it as an epidemic or outbreak.

[2]K.K. Thomas, "40 Years in a Post-Smallpox World," Johns Hopkins Bloomberg School of Public Health, May 8, 2020 (https://publichealth.jhu.edu/2020/40-years-in-a-post-smallpox-world).

[3]CDC's National Center for Health Statistics COVID-19 death counts in the U.S. are based on provisional counts from death certificate data, which do not distinguish between laboratory-confirmed and probable COVID-19 deaths. Provisional counts are incomplete because of an average delay of 2 weeks (a range of 1–8 weeks or longer) for death certificate processing. See CDC, National Center for Health Statistics, "Provisional Death Counts for Coronavirus Disease 2019 (COVID-19)," accessed January 10, 2023, https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm.

[4]R. Bruns and N. Teran, "Weighing the Cost of the Pandemic," Institute for Progress, April 21, 2022: 1-7 (https://progress.institute/weighing-the-cost-of-the-pandemic/).

[5]Determination of a pandemic's origin has some level of inherent scientific uncertainty. For this report, we use the term "origin" to mean "likely origin," acknowledging this uncertainty.

caused the 2002-2003 SARS pandemic.[6] However, the knowledge gained from those investigations helped researchers more quickly determine the origin of the MERS outbreak of 2012, according to literature we reviewed.

You asked us to conduct a technology assessment to understand how the U.S. can be better prepared to predict, prevent, detect, assess, and effectively respond to future pandemics, with a focus on determining the origins of pandemics. In this technology assessment, we describe

- key technologies available for pandemic origin investigations;
- strengths and limitations of these tools and how researchers use them to investigate pandemic origins;
- cross-cutting challenges researchers face in trying to determine a pandemic's origin; and
- policy options that may help address the cross-cutting challenges of using these key technologies to determine the likely origin of a pandemic.[7]

To address our objectives, we conducted literature searches and reviewed selected scholarly articles and other documents, including reports from the Centers for Disease Control and Prevention (CDC), Office of the Director of National Intelligence, the Johns Hopkins Center for Health Security, World Health Organization, and select national laboratories, describing technologies for pandemic pathogen characterization. Additionally, we interviewed stakeholders and experts with a diverse set of perspectives on the science and application of these technologies. This included holding an expert meeting with assistance from the National Academies of Sciences, Engineering, and Medicine. See appendix I for more information on our scope and methodology and appendix II for a list of participants in our expert meeting.

We conducted our work from August 2021 through January 2023 in accordance with all sections of GAO's Quality Assurance Framework relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

[6]Initial evidences showed the civet cat to be the primary animal origin of the SARS-associated coronavirus (SARS-CoV). Later studies suggested that Chinese horseshoe bats were natural reservoirs—locations where the pathogen circulates among people and animals between outbreaks—and that the civet cat most likely served as an intermediate host. However, the study identifying the closest ancestor to SARS-CoV in a single bat colony in the Kunming, Yunnan Province in China was not published until December 2015.

[7]For the purposes of this report, the term "technologies" includes the instruments, techniques, skills, methods, and processes used in pathogen characterization.

1 Background

Pandemics are global infectious disease outbreaks that can greatly increase morbidity and mortality in people, and cause significant economic and social disruptions. According to the scientific literature, most pandemics where the origin is known were caused by the natural transmission of a virus through animal-to-human contact. Outbreaks have also been reported as a result of laboratory accidents, and research suggests the 1977-1978 H1N1 influenza pandemic may have been the result of a laboratory accident or other cause (see fig. 1).[8] Determining the likely origin of pandemics is challenging and requires information gathered from established methods for the investigation of disease outbreaks.

1.1 Natural origin

A pandemic with a natural origin scenario could initiate with the accidental infection of one or more individuals by a pathogen transmitted from animals, including via insects or other sources such as the environment. Pandemics are often the result of zoonotic pathogens being naturally transmitted between animals and humans.[9]

Zoonotic diseases can have several potential outcomes:

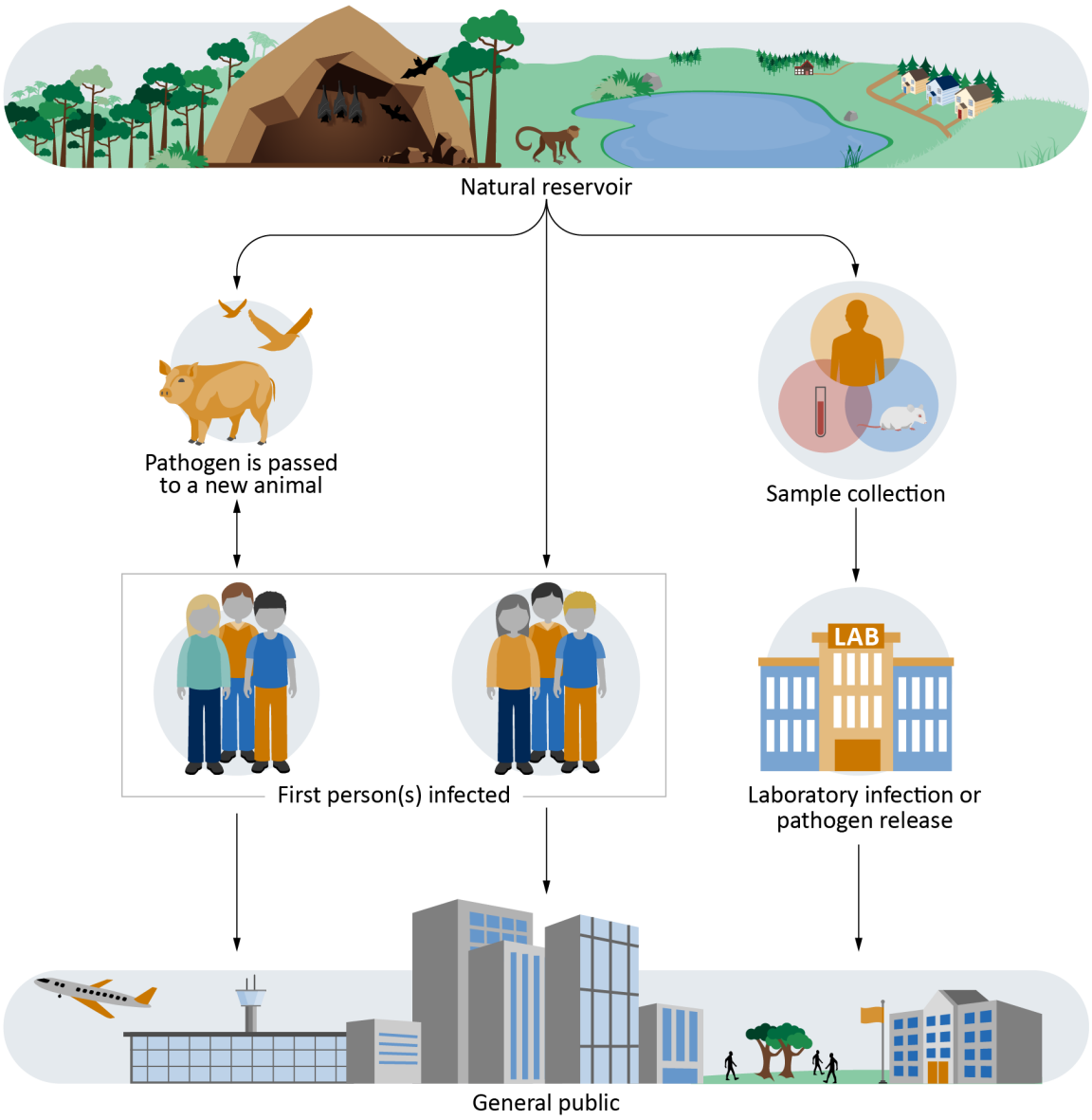
- the pathogen infects animals or humans, where it may or may not cause disease;
- the pathogen adapts so that it can be transmitted to humans without sustained human-to-human transmission, resulting in only small outbreaks among people; or
- the pathogen adapts for sustained transmission among humans, resulting in outbreaks, epidemics, pandemics, or becoming endemic in the human population.[10]

[8]Examples of known laboratory accidents involving pathogens include the unintended release of smallpox virus from a laboratory in the United Kingdom in 1978, which resulted in one death and over 300 vaccinations and surveillance of the researcher's close contacts; the accidental self-injection of the Ebola virus by a Russian scientist in 2004 that resulted in her death; and the unintended release of *Brucella* bacteria from a vaccine facility in China that began in 2019, continued in 2020, and caused over 10,000 infections. Other causes suggested for the 1977-1978 H1N1 influenza pandemic include deliberate release of the virus or a vaccine trial mishap. See M. Rozo and G.K. Gronvall, "The Reemergent 1977 H1N1 Strain and the Gain-of-Function Debate," *mBio*, vol. 6 (2015):e01013-15.

[9]Zoonotic "spillover" refers to the transmission of a pathogen from animals to humans. Zoonotic "spillback" refers to the transmission of a pathogen from humans to animals and is sometimes referred to as "reverse zoonosis."

[10]CDC describes endemic as the constant presence or the usual prevalence of a disease or infectious agent in a population within a geographic area. Adaptation of a pathogen to a new host is not an absolute requirement for transmissibility among humans.

Figure 1: Examples of pandemic origin scenarios



Source: GAO. | GAO-23-105406

Note: These pandemic origin scenarios are not meant to be exhaustive. Other scenarios may be possible. For example, researchers could be accidently infected from the environment during sample collection or during sample packaging or shipment. In the laboratory origin scenario depicted in the right column, the "first person(s) infected" may occur during sample collection, in the laboratory, or in the general public.

We identified three main factors that affect the risk of zoonotic transmission: the animals that harbor the pathogen, the nature of human interaction with those animals, and the frequency of those interactions. Scientific literature suggests that the likelihood of zoonotic disease spillover has increased in recent decades likely because of factors such

as increases in human-animal interactions through farming practices, wildlife trade, habitat loss, and climate change. These interactions facilitate the repeated exchange of pathogens between animals and humans.[11] However, most pathogens that infect humans through zoonotic transmission do not result in significant human-to-human transmission.

The exact processes by which some pathogens adapt to infect humans and then maintain long-term human-to-human transmission are not well understood, limiting our ability to quickly or definitively establish the origin of a pandemic. For example, the origins of the Ebola virus and SARS-CoV-2, which causes COVID-19, remain inconclusive. Even established, well-understood pathogens may adapt to expand beyond their typical disease geography, become more transmissible, or cause more severe disease. Although most pathogens could evolve or be manipulated in ways that may cause a human pandemic, viruses—especially RNA viruses—are the most likely to have this ability.[12]

Further, the location of the first reported human disease case—also known as the index case—might differ from where the pathogen naturally resides, making it difficult for researchers to identify a pandemic's actual origin.

1.2 Laboratory origin

A pandemic with a laboratory origin scenario could initiate with either the accidental infection of an individual or individuals by a pathogen in a laboratory setting, or infections caused by an accidental or intentional release of the pathogen from a laboratory. For example, such an infection could occur when a researcher collects a sample containing a pathogen and transfers it to a laboratory.[13] During the course of handling the pathogen, the researcher may accidently be exposed to the pathogen and become infected. Alternatively, laboratory containment may break down, resulting in the accidental release of the pathogen into the surrounding environment and infection of individuals outside the laboratory.[14] Further, some infections with a laboratory origin could involve the intentional modifications of

[11]The repeated exchange of pathogens between animals and humans is also known as "viral chatter." The frequency of viral chatter is high on farms where wild and domesticated animals are housed and bred together as well as in live animal and wet markets. Live animal and wet markets sell perishable items—such as fresh meat and produce—and sometimes live animals which are often slaughtered on-site.

[12]A. Adalja et al., "Characteristics of Microbes Most Likely to Cause Pandemics and Global Catastrophes," *Current Topics in Microbiology and Immunol*ogy, vol. 424 (2019):1-20.

[13]A sample may be obtained from human or animal sources (e.g., blood, saliva, or tissues), the environment (e.g., water, soil, or air), food, or other sources. The sample may contain the pathogen or markers—such as antibodies—indicating pathogen exposure or infection.

[14]For example, in 1979, anthrax spores were accidentally released from a facility in the Soviet city of Sverdlovsk. The cloud of spores produced a 50-kilometer trail of disease and death in animals and humans—at least 66 people died. J.W. Sahl et al., "A *Bacillus anthracis* genome sequence from the Sverdlovsk 1979 autopsy specimens" *mBio* (2016) 7(5): e01501-16.

pathogens created using techniques such as genetic engineering or serial passaging.[15]

1.3 Investigating pandemic origin

Several key technologies and approaches can help inform a pandemic's origin. Researchers typically rely on samples and data obtained from infected people, animals, and the environment. For example, researchers may collect clinical samples from infected individuals or samples from animals in or around outbreak areas such as farms or live animal or wet markets. Researchers may also collect environmental samples—such as water, soil, or insects—in or around outbreak areas. Data may consist of information about the infected individuals collected during case investigation activities—including travel history and prior contacts with other infected people—to help determine disease spread. Data may also include pathogen genetic sequence information and how the pathogen infects or transmits between hosts.[16]

Chapters 2 and 3 of this report describe the key technologies—including their strengths and limitations—used to characterize pathogens and assist in pandemic origin investigations. Chapter 4 discusses the cross-cutting challenges researchers face when investigating the origin of a pandemic.

Chapter 5 presents five policy options that may help address these challenges and improve the ability of researchers to respond more quickly and effectively to future pandemics.

[15]Genetic engineering uses laboratory-based technologies to alter the genetic makeup of a pathogen. For example, genetic engineering may involve adding a gene from one species to an organism from a different species to produce a desired trait. Serial passaging involves iteratively growing a pathogen in animals or cell cultures in a laboratory. Over time, the pathogen could acquire mutations similar to those that arise in natural environments. Cell culture involves isolating and growing animal or plant cells in a laboratory environment. Some pathogens, such as viruses, infect and replicate inside the cells. GAO has work underway examining the Department of Health and Human Services' oversight of research involving enhanced potential pandemic pathogens.

[16]A pathogen's genetic sequence—also known as the genome—comprises the order of the chemical "letters" of a pathogen's genetic material—DNA or RNA (genomes of some viruses only contain RNA). DNA and RNA contain all of the pathogen's genetic information. For the purposes of this report, the term "sequence" refers to "genetic sequence," and the term "genetic databases" refers to "genetic sequence databases."

2 Technologies for Investigating Pandemic Origin

Several key technologies can help inform a pandemic's origin. Drawing on information from experts, stakeholders, and scientific literature, we identified the following categories of such technologies:

- genetic sequence analysis;
- pathogen exposure monitoring and disease tracking; and
- laboratory-based pathogen studies.

2.1 Genetic sequence analysis

Genetic sequence analysis involves the combination of pathogen genomic sequencing, bioinformatics analysis, and genetic databases. These technologies allow researchers to generate, analyze, and compare a pathogen's genetic makeup—its sequence—against other pathogen sequences (see fig. 2).[17]

After generating the sequence of the pathogen, researchers use different bioinformatics tools to piece together and analyze the compiled sequences. While many analyses compare the sequences against those in genetic databases, other analyses can be performed independent of the databases.

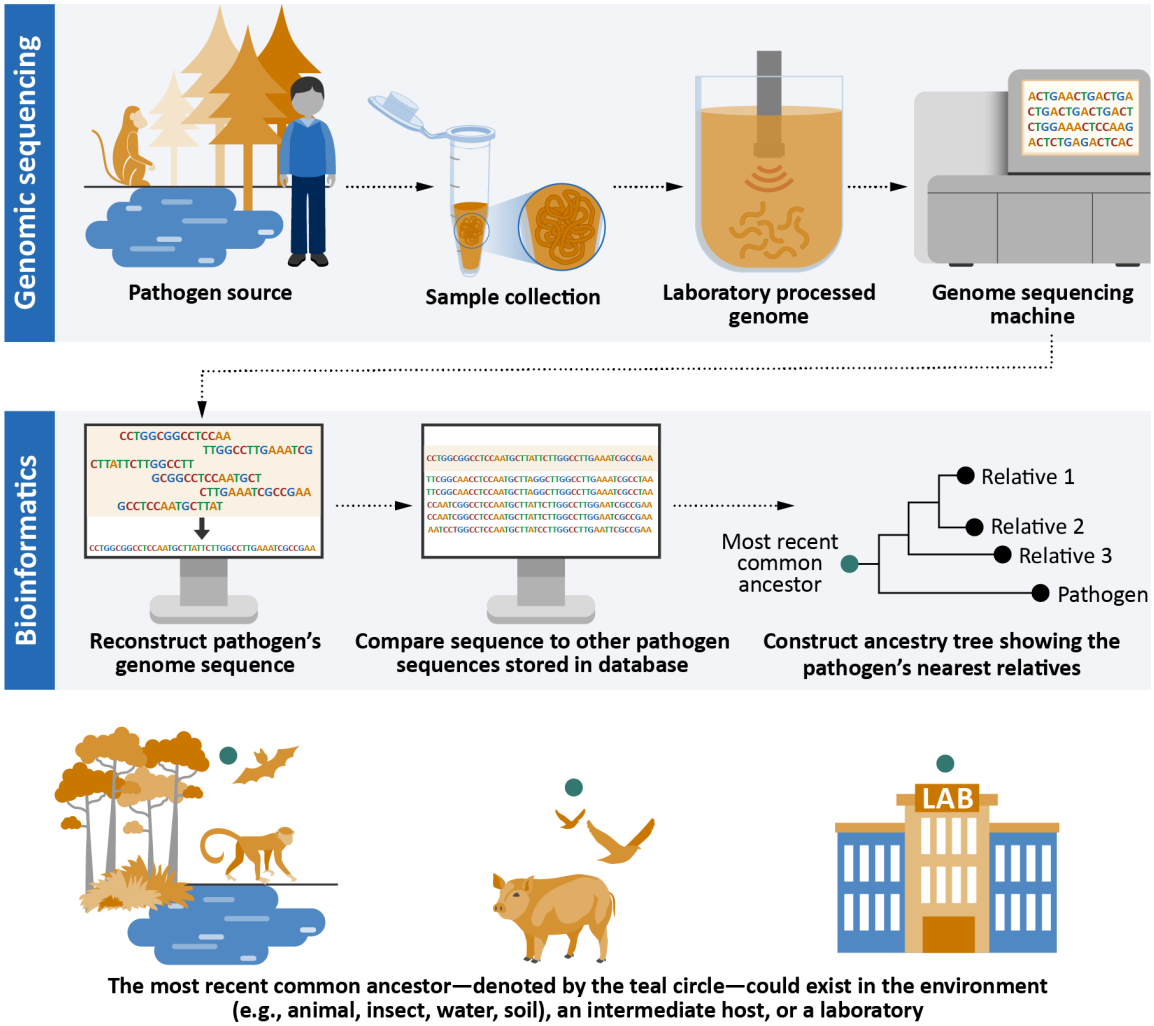
Genomic sequencing. Genomic sequencing identifies the order—or sequence—of the chemical "letters" of a pathogen's genetic material.[18] One traditional sequencing method—Sanger sequencing—copies specific segments of the pathogen's genetic material repeatedly, marks the copies with fluorescent molecules, sorts them, and then reads the individual letters.[19] Sanger sequencing produces accurate data. Reconstructing complete pathogen genomes, which are thousands to millions of letters in length, letter by letter is slow and expensive.

[17]Bioinformatics is an interdisciplinary field that uses computational algorithms for the analysis of biological data—in this case, genetic sequences.

[18]Each of the four letters—A, C, G, and T (or U in the case of RNA)—represents a chemical unit of DNA or RNA called a base.

[19]See GAO, *Science & Tech Spotlight: Genomic Sequencing of Infectious Pathogens,* GAO-21-426sp (Washington, D.C.: Mar. 30, 2021).

Figure 2: Genetic sequence analysis for pandemic origin investigations



The most recent common ancestor—denoted by the teal circle—could exist in the environment (e.g., animal, insect, water, soil), an intermediate host, or a laboratory

Source: GAO. | GAO-23-105406

Next-generation sequencing technologies can process hundreds of genomes simultaneously, enabling researchers to generate large amounts of pathogen sequence data more quickly than Sanger sequencing. Most next-generation sequencing technologies use a "massively parallel" approach to generate many short sequences of letters from different parts of the pathogen's genome at the same time. Assembling the short sequences then produces the entire sequence of the pathogen's genome.

Another next-generation sequencing technology—nanopore sequencing—uses an electrical current to thread single DNA or RNA strands through tiny pores of a membrane. As the DNA or RNA strand passes through the pore, the electrical field varies based on the specific sequence passing through the pore. By measuring and analyzing variations in the electrical field, the technology can sequence long stretches of the DNA or RNA strand.

Bioinformatics. Researchers use many types of bioinformatics tools to analyze genomic sequences. One type assembles the stretches of DNA or RNA generated by next-generation sequencing instruments to reconstruct the pathogen's genome. A second type compares the pathogen's genetic sequence to sequences stored in genetic databases.[20] Some of these tools allow researchers to analyze the structural and functional information of a gene or protein from the sequences. These tools may also identify mutations in the sequences and potential genetically-engineered sequences. A third kind of tool analyzes genetic sequences to identify likely evolutionary relationships between pathogens and their nearest relatives. This process is known as phylogenetic analysis.

Genetic databases. Researchers use genetic databases to organize the biological information gathered from many different types of pathogens.[21] Many of these genetic databases contain millions of sequences from thousands of pathogens, allowing users to compare genetic sequences of a given pathogen against many other pathogens that were previously catalogued.[22]

2.2 Infectious disease surveillance

Other tools can help researchers understand the path of the disease. The study of the presence of antibodies in the blood in response to pathogens, serology, enables the characterization and monitoring of pathogen infections in human and animal populations.[23] Serology can help establish whether a human or animal has been infected by a pathogen, sometimes long after the initial infection. Examples of technologies used for serology include biological and chemical tests.[24]

Epidemiology—the study of disease occurrence in humans and animal populations—provides information about the timing and geographic spread of the disease. Epidemiological surveillance tracks disease in populations to try to determine when and where the disease originated, among other things.[25] For example, epidemiology may help identify the source of the pathogen, its possible spread, and possible "reservoirs"

[20]Bioinformatics tools, such as the National Center for Biotechnology Information's (NCBI) Basic Local Alignment Search Tool (BLAST), identify similarities between nucleic acid or amino acid sequences. BLAST also scores the statistical degree of similarities between the sequences. Higher scores indicate a higher degree of similarity—or likely relatedness—between sequences. For more information, see S.F. Altschul et al., "Basic Local Alignment Search Tool," *Journal of Molecular Biology,* vol. 215 (1990): 403-410.

[21]This information includes DNA, RNA, and amino acid sequences from organisms collected from the environment and research conducted in laboratories. Amino acids are the fundamental building blocks of proteins.

[22]Examples of genetic databases include GenBank®, European Nucleotide Archive (ENA), DNA Data Bank of Japan (DDBJ), and Global Initiative on Sharing All Influenza Data (GISAID).

[23]An antibody is a protein component of the immune system that circulates in the blood, recognizes foreign substances like bacteria and viruses, and neutralizes them. The percentage of individuals in a population whose blood contains antibodies to a pathogen is called seroprevalence.

[24]For example, an enzyme-linked immunosorbent assay (ELISA) detects host antibodies by binding to pathogen proteins—called antigens—coated in wells on test plates. The presence or absence of these antibody-antigen complexes can then be determined using enzymes. A chemiluminescent immunoassay (CLIA) uses chemical probes that detect and label antibodies by generating light emissions (i.e., luminescence) through a chemical reaction.

[25]According to CDC, epidemiological surveillance is the ongoing and systematic collection, analysis, and interpretation of health data in the process of describing and monitoring a health event.

where the pathogen circulates among people and animals between outbreaks.

2.3 Laboratory-based pathogen studies

Laboratory-based pathogen studies examine interactions between the pathogen and the host animal or person infected with the pathogen. Such studies can reveal how pathogens infect hosts and are transmitted from one host to another. The results of these studies help researchers understand the distribution and spread—epidemiology—of the disease caused by the pathogen. Researchers also study the degree to which a pathogen can infect and transmit between hosts using animals known as *in vivo* studies, or cell cultures known as *in vitro* studies. For example, laboratory-based pathogen studies may use animals and cell cultures to determine a pathogen's transmission rate between infected and uninfected animals and cells as well as the pathogen's infectious dose.

Experts told us that other laboratory-based technologies may enable researchers to identify modifications to nucleic acids or proteins. These technologies include proteomics, the study of host and pathogen proteins; glycomics, the study of sugar molecules occurring on proteins; and epigenetics, the study of chemical modifications to host or pathogen nucleic acids—see text box for further explanation. The information gained from these technologies could help researchers in pandemic origin investigations; however, these technologies are not fully developed for such use.

Epigenetics

Researchers use epigenetics to study how behavior and the environment may cause changes in DNA and RNA that affect genes and proteins. For example, DNA and RNA may be modified through the addition of chemical groups. Typically, these chemical groups occur at specific places on the DNA and RNA. The modifications affect the ability of enzymes to "read" the DNA and RNA and produce proteins, resulting in cellular changes.

Experts and literature note that certain pathogens can cause epigenetic changes in infected people; some ongoing research is focused on detecting whether exposure to certain biological agents can be identified by examining such epigenetic changes. Further, one expert noted that it is not yet possible to detect laboratory manipulation-based epigenetic changes, but epigenetics may offer this capability for future origins investigations.

Source: GAO review of literature and the March 2022 expert meeting. | GAO-23-105406

3 Researchers Have Used a Variety of Technologies for Pandemic Origin Investigations

Researchers have used a variety of technologies for pandemic origin investigations. For example, researchers have generated pathogen sequence data using genomic sequencing, then used bioinformatics tools to analyze and compare the sequence to reference sequences stored in genetic databases. Three outcomes can result from these comparisons:

- If a pathogen's sequence matches sequences from naturally-occurring organisms, this could provide support for a natural origin. Further, phylogenetic analyses may be conducted to identify the pathogen's closest relatives or its most recent common ancestor.[26]
- If a pathogen's sequence, or parts of its sequence, matches known, laboratory-generated sequences, this could provide support that a pathogen may have a laboratory origin.
- If a pathogen's sequence does not closely match any sequences in the genetic databases, this could indicate a novel pathogen. This could also indicate the genetic databases lack the diversity of sequences needed to accurately compare the pathogen's sequence.

Other approaches, such as serology, epidemiology, and laboratory-based pathogen studies, have also been used to support such pandemic origin investigations. However, multiple lines of evidence are often needed to establish a pandemic's likely origin. Further, experts told us technologies are not the limiting factor for investigating the likely origin of a pandemic.

3.1 Researchers used genetic sequence analysis to determine the likely origin of several pandemics

Researchers used genetic sequence analysis to help establish the likely natural origins of several pandemics and outbreaks, including the 2002-2003 SARS pandemic, the 2009 H1N1 influenza pandemic, and the initial MERS outbreak in 2012.[27] Researchers also

[26]The most recent common ancestor of any set of individuals—such as viruses—is the most recent individual virus from which all of the other individual viruses in the group are directly descended. This definition is adapted from the International Society of Genetic Genealogy.

[27]Genetic sequence analysis of samples from civet cats and a raccoon dog from a live animal market showed that the animal SARS-CoV strains were 99.8 percent identical to the SARS-CoV strains isolated from infected humans. See L.-F. Wang and B.T. Eaton, "Bats, civets and the emergence of SARS," *Current Topics in Microbiology and Immunology*, vol. 315 (2007):325-344. Genetic sequence analysis also showed that MERS-CoV strains isolated from camels were almost identical to those isolated from humans and were phylogenetically related to bat coronaviruses. See J. Cui et al., "Origin and evolution of pathogenic coronaviruses," *Nature Reviews Microbiology*, vol. 17 (2019): 181-192. Genetic sequence analysis of samples from humans and pigs established the origin of the H1N1 influenza virus in central Mexico, where it jumped from pigs to humans. See I. Mena et al., "Origins of the 2009 H1N1 influenza pandemic in swine in Mexico," *eLife* (2016) 10.7554/eLife.16777.

used phylogenetic analysis to trace the transmission of HIV-1 from Africa to Haiti, followed by its subsequent transmission from Haiti to North American populations around the 1960s. Researchers continue to use genetic sequence analysis to investigate the origin of other pandemics, including the COVID-19 pandemic caused by SARS-CoV-2.[28]

The increasing speed and accuracy and decreasing cost of genomic sequencing technologies, such as next-generation sequencing, allow researchers to simultaneously process hundreds of pathogen genomes. Researchers are thus able to quickly generate pathogen sequence data necessary for investigating potential origin**.** Experts told us that because of these strengths, they consider genomic sequencing a key technology for pandemic origin investigations.

A key limitation of genetic sequence analysis is that some laboratory-based genetic modifications may be indistinguishable from natural variations. For example:

- Some traditional genetic engineering techniques and newer genome editing tools—such as CRISPR-Cas9—may leave no detectable trace of genetic modification.[29] Some bioinformatics tools that use artificial intelligence (AI) may help researchers detect patterns indicative of genome editing.[30] However, these are currently limited by a lack of large sequence datasets on which to train the algorithms.
- One agency official described a 2011 large foodborne outbreak in Germany that was caused by a strain of *Escherichia coli* (*E. coli*) bacteria. Genetic sequence analysis showed the strain contained genetic sequences from two strains of *E. coli*. This unusual genetic makeup potentially supported a laboratory origin. However, researchers later determined, through additional research, that a natural origin was more likely.
- Sequence changes (i.e., mutations) resulting from laboratory adaptation experiments—such as serial passaging—may be more difficult to detect than genome editing because the laboratory adaptation more closely mimics aspects of natural processes of evolution. For example, some researchers argue that serial passaging may explain certain features of the SARS-CoV-2 genome, while others argue that a zoonotic origin is the more likely explanation for those features.[31]

Some phylogenetics software tools are limited in their utility for assessing pathogen origins because of technical limitations of the

[28]J.E. Pekar et al., "The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2," *Science* (2022) 10.1126/science.abp8337; M. Worobey et al., "The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic," *Science* (2022) 10.1126/science.abp8715.

[29]Clustered Regularly Interspaced Palindromic Repeats (CRISPR)-associated protein number 9 (Cas9) is one type of genome editing technology that allows scientists to precisely modify a pathogen's genome, potentially leading to changes in a pathogen's characteristics.

[30]E.C. Alley et al., "A machine learning toolkit for genetic engineering attribution to facilitate biosecurity," *Nature Communications* (2020) 10.1038/s41467-020-19612-0.

[31]K.G. Andersen et al., "The proximal origin of SARS-CoV-2," *Nature Medicine*, vol. 26 (2020): 450-455.

analysis programs and deficiencies in databases used for sequence comparisons. For example, some phylogenetic tools use a certain pattern of pathogen evolution from other organisms when comparing sequences. However, many pathogens do not follow the types of evolutionary patterns that other organisms follow. As a result, conclusions based on the use of these tools should be confirmed with other methods. More recently, network-based approaches have been used to reconstruct virus evolution more realistically.

Additionally, some phylogenetic tools are not capable of analyzing the millions of sequences currently being generated. For example, one expert told us that the volume and complexity of SARS-CoV-2 data crashed a commonly used phylogenetics program. The lack of reference sequences and metadata in databases also impacts researchers' ability to conduct meaningful phylogenetic analyses.[32]

Further, multiple experts told us that it can be problematic when databases have sequences overrepresented by specific countries. For example, the SARS-CoV-2 sequences in the Global Initiative on Sharing All Influenza Data (GISAID) database are dominated by data from the U.S. and U.K., whereas data from relevant locations elsewhere in the world are scarcer. This underrepresentation negatively affects the ability to determine where a pathogen may have originated.

3.2 Researchers used serology and epidemiological surveillance for pandemic origin investigations

Researchers have also used serology and epidemiological surveillance to monitor pathogen infection and disease occurrence in human and animal populations to support pandemic origin investigations. Serology and epidemiological surveillance can provide information regarding the timing and geographic spread of the pathogen and disease. For example, if serology studies detect antibodies in animal populations near a suspected disease outbreak in humans where the disease is not normally present or expected, this could lend support to a natural origin. Further, epidemiological surveillance can be used to generate models to predict how a pathogen spreads. These models can also be run in reverse to trace the spread of the disease back to the early stages of a pandemic. However, for serology and epidemiological surveillance to be effective in determining a pandemic's origin, investigators need access to samples and data from infected or exposed individuals from early in an outbreak and as close to index cases as possible to reliably trace the disease back to the first human infection(s).

Serology surveillance in people and camels provided two key pieces of information that contributed to the determination that camels were direct sources of human infection with MERS-CoV. First, researchers detected MERS-CoV antibodies from archived camel blood samples dating back to 1983. Second,

[32]In this report, we refer to information about genetic sequences, such as when and where a sample was collected, as metadata.

serology surveillance showed a higher prevalence of MERS-CoV antibodies in humans exposed to camels relative to the general population. Together with other studies, this information led researchers to conclude that MERS-CoV was likely transmitted to people from camels.

Epidemiological studies of the first SARS cases in Guangdong Province, China in 2002-2003 suggested a zoonotic origin of the virus. For example, several of the early cases were associated with occupations that involved contact with wildlife, including handling, killing, and selling wild animals as well as preparing and serving wildlife animal meat in restaurants. Subsequent serology surveillance found a higher than normal seroprevalence of SARS-CoV antibodies among wild animal traders as compared to vegetable traders from the same Guangdong market. Further, serology surveillance of animal traders in three different live animal markets found that 13 percent had SARS-CoV antibodies, whereas 72 percent of traders of civet cats had SARS-CoV antibodies.[33]

Researchers also used epidemiological data, among other types of data, to investigate the hypothesis that the COVID-19 epidemic in Wuhan began at the Huanan market. Based on the geographic and timing patterns of reported cases within the city and the specific locations of cases within the Huanan market, recent studies assessed that this market was "an early and major epicenter" of COVID-19 emergence.[34] However, researchers and agency analysts reported that uncertainty still exists about where the first SARS-CoV-2 infections occurred because of a lack of clinical samples available for serological and genetic analyses as well as a lack of epidemiological data from the earliest cases.[35]

Serology and epidemiological surveillance may be limited by the ability to collect and analyze samples from infected humans and animal populations. For example, certain countries may refuse or limit researchers' access to field sites, facilities, data, or people. Further, researchers conducting field-based sample collections may encounter logistical and operational barriers to accessing remote field sites, including personal protective equipment constraints.[36] Sensitive and specific serology tests may also take time to develop and validate.

Researchers may also face technical challenges for collecting, preserving, and transporting samples. For example, many viruses, such as SARS-CoV-2, only contain RNA, which is less chemically stable than DNA, and may require specialized preservatives. Samples may also require cold storage and shipment—known as cold chains—to maintain their integrity. In remote parts of the world, cold chain infrastructure

[33]L.-F. Wang and B.T. Eaton, "Bats, Civets and the Emergence of SARS," *Current Topics in Microbiology and Immunology,* vol. 315 (2007): 325–344.

[34]E.C. Holmes et al., "The Origins of SARS-CoV-2: A Critical Review," *Cell,* vol. 184 (2021): ep. 1-9.

[35]Office of the Director of National Intelligence, National Intelligence Council, "Updated Assessment on COVID-19 Origins" (2021): ep. 1-18.

[36]Collecting animal samples can be dangerous both to the individual researchers collecting the samples as well as the public. To collect samples, researchers typically need to make personal contact with animals. One expert told us about a project that uses drones or robots to collect guano samples from bat caves, mitigating the possibility of researchers contracting viruses by eliminating the need to enter the caves themselves.

may be lacking. Further, samples collected from humans or animals have high amounts of host genetic material, making it difficult or more time-consuming to extract, isolate, and analyze a pathogen's genome.

Finally, even comprehensive field-based sampling aimed at investigating the origins of pandemic pathogens may be inconclusive. For example, researchers recently reported a sampling effort in China aimed at tracing the origin of two pandemic pathogens, SARS-CoV and SARS-CoV-2.[37] Despite generating a database of over 17,500 animal samples, researchers did not find any closely related coronaviruses.

3.3 Researchers used laboratory-based pathogen studies for pandemic origin investigations

Laboratory-based pathogen studies using cell cultures or animals have generated information about a pathogen's ability to infect, mutate, adapt to, and spread between hosts. Results from these laboratory studies provided evidence supporting known natural patterns of spread or unusual patterns of spread indicative of a possible laboratory-related origin. For example, researchers studying pandemic H1N1 influenza virus in ferrets identified the viral genes, proteins of transmission, and host receptor sites that drive different routes of transmission.[38] The results of these studies supported the conclusion that this virus likely originated from animal-to-human transmission.

Several cell culture and animal studies have also been used for studying SARS-CoV-2 infection and spread. For example, researchers used cell cultures to isolate and study the virus samples from some of the first COVID-19 patients and to identify host factors required for SARS-CoV-2 replication. Researchers also used cell cultures to study genetic changes in the virus during serial passaging, including confirming the ability of the virus to adapt quickly to the host. Further, researchers used different animal studies to determine the ability of the virus to transfer to and infect healthy animals, which may provide evidence for the virus reservoir and intermediate hosts.

Laboratory-based pathogen studies are useful for studying pathogen biology under highly controlled conditions. Cell culture studies and animal studies each have strengths. Cell culture studies comply with the ethical desire for reducing the use of animals, and they are less expensive, faster, and allow for the study of specific pathogen-host targets, which could not be assessed in humans or animals. Animal studies help researchers better understand pathogen infection and transmission, and they have the potential to elucidate the natural history of the disease.

Key limitations of laboratory-based pathogen studies are that some pathogens cannot be easily cultured in a laboratory setting, and some pathogens require enhanced biosafety-level facilities. Results from controlled laboratory transmission studies also may not accurately represent the natural environment, making it difficult for

[37]Z. Wu et al., "A Comprehensive Survey of Bat Sarbecoviruses across China for the Origin Tracing of SARS-CoV and SARS-CoV-2," *Research Square* (2021): ep. 1-37.

[38]J.S. Long et al., "Host and viral determinants of influenza A virus species specificity," *Nature Reviews Microbiology* (2019) 10.1038/s41579-018-0115-z.

researchers to clearly distinguish between natural versus laboratory-controlled transmission patterns. For example, cell culture studies do not resemble the complexity of a human or animal host, and translating cell culture-generated data to animal models can be particularly challenging. Further, animal studies are costly and raise ethical concerns.

4 Researchers Face Three Key Challenges When Investigating Pandemic Origin

In addition to the specific technology limitations discussed earlier, researchers also encounter three challenges at various stages in the pandemic origin investigation process, according to experts. Specifically,

- Lack of sufficient access to samples and genetic sequence data,
- Lack of standardized processes for submitting, accessing, and using genetic sequence data stored in databases around the world, and
- Lack of a sufficient and skilled interdisciplinary workforce.[39]

4.1 Researchers lack sufficient access to critical samples and data

We found that access to samples from index cases and other primary and secondary cases or genetic sequence data derived from those samples may be restricted in two broad ways.

- Local concerns may limit access to samples and data. For example, primary care physicians may not collaborate with public health officials. Therefore, data from medical testing and patient care may not be available for pathogen surveillance. Privacy concerns, general mistrust, perceived infringements on a country's sovereignty, or fear of negative consequences can also result in restricted access.
- Even if researchers have access to samples and data, their ability to extract suitable information may be limited by a lack of standardized processes. For example, health officials may collect samples for a purpose other than pathogen surveillance or store and process the data obtained from the samples in a way that precludes investigations into the origin of the pandemic. Further, no one entity is responsible for determining and enforcing standardized processes.

Experts told us that multilateral agreements on sample and data sharing are necessary because pandemics can originate from anywhere and rapidly spread internationally. They also said that negotiating or modifying agreements each time a pandemic occurs is not effective.

[39]Sufficient and prompt access to initial outbreak samples enables actions to prevent current disease spread (e.g., via travel restrictions, testing programs, vaccine development). However, for pandemic origin investigations, which may occur months or years after the initial outbreak, sufficient and timely access to such samples is important to maximize the chances of a reliable result.

4.2 Lack of standardized processes for genetic sequence databases prevents researchers from analyzing data effectively

Some genetic sequence databases used by researchers may lack standardized processes for data submission, access, and use. To investigate the origin of a pandemic, researchers need access to genetic sequence data, which may be stored in multiple databases, such as the National Center for Biotechnology Information's (NCBI) GenBank®, GISAID, and the European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI).[40] Experts cited three main challenges to working across multiple databases:

- Each genetic sequence database may have different processes for submitting, accessing, and using the data. GenBank, which is one of the most widely used databases, is open access, places no restrictions on the distribution of data, and provides multiple submission tools depending on the type of sequence data to be submitted. GISAID, on the other hand, requires personal access credentials, prohibits any re-distribution of data, and provides a web portal for submissions. As a result, gathering all of the data necessary to investigate the origin of a pandemic can be challenging.
- Genetic sequence databases generally lack standardized user interfaces for data submission and access, and some existing user interfaces can be cumbersome. For example, experts told us that submission processes for some major genetic sequences databases are not user-friendly, and previous submissions can be difficult to edit.[41] Similarly, interfaces for accessing data are not standardized. For example, some major databases lack application programming interfaces (API) that would provide access to the data from other applications.[42] Because researchers lack standardized submission and access interfaces, they may have to use different procedures to submit and retrieve needed data from relevant databases, which can be time-consuming and inefficient.
- Metadata are crucial for investigating the origin of a pathogen, but their availability and quality may vary. For example, GenBank's submission process allows researchers to submit information in distinct metadata fields with few constraints on content. One record that we examined lists "Japan" as the country where the sample was collected and "2020-07" as the collection date. Another

[40]GenBank is part of the International Nucleotide Sequence Database Collaboration, which includes the DNA DataBank of Japan (DDBJ), the European Nucleotide Archive (ENA), and GenBank. These three databases exchange data on a daily basis.

[41]For example, experts told us that GenBank allows only the original author to edit a submission. This could be problematic if an error to the record exists and the original author is no longer active in research. In this case, the error may become permanent. However, the National Institutes of Health noted a record cannot be publicly released in GenBank until it has a valid scientific classification. Further, if an organism's valid scientific classification is revised by an international standards group, then the record can be updated accordingly without requiring a submitter request.

[42]An application programming interface (API) enables machine-to-machine communication, allowing users to obtain real-time data updates. GAO, *Open Data: Treasury Could Better Align USAspending.gov with Key Practices and Search Requirements*, GAO-19-72 (Washington, D.C.: Dec. 13, 2018).

record of a different genetic sequence lists a more specific location, "Canada: Toronto," as the country where the sample was collected, but no collection date. Although GenBank allows users to report the latitude and longitude where samples were collected, a 2017 study estimated that 99 percent of records do not include that information.[43]

These challenges may be exacerbated by the immense scale and continued growth of genetic sequence data. (See text box for a prediction on the future growth of genomic data.) As the amount of data in each database grows, and as more databases are added, standardized processes are crucial to ensure that researchers can compile, analyze, and share all the genetic sequence data necessary to investigate the origin of a pandemic. However, it is unclear if the existing infrastructure of multiple independent databases worldwide can support the growth of genomic data.

Rapid growth of big data

A 2015 study predicted that, by 2025, genomics research worldwide will generate between 2 and 40 exabytes of data annually. (For reference, 1 exabyte equals 1 billion gigabytes.) This would make genomics one of the most challenging domains of Big Data in terms of data acquisition, storage, distribution, and analysis.

Accommodating the expected growth of genomic data will require advancements in computational speed and power, as well as algorithms optimized for Big Data.

Source: GAO review of literature. | GAO-23-105406

4.3 The global research community lacks a sufficient and skilled interdisciplinary workforce

Pandemic origin investigations require a highly skilled workforce with expertise in multiple fields. We identified four main challenges to developing and retaining such a workforce based on information we gathered from experts and literature:

- Demand for workers in relevant fields tends to increase when pandemics occur and decrease when pandemics end. Likewise, funding for relevant research tends to fluctuate. This makes it challenging to keep the workforce "warm" (i.e., available and proficient) to conduct investigations promptly when pandemics occur.
- Pandemic origin investigations require expertise in multiple fields such as biology, virology, microbiology, immunology, epidemiology, ecology, genomics, bioinformatics, and computer science. However, the current workforce is siloed because of factors such as academic structures, funding priorities, and grant processes, according to experts we interviewed.[44] This makes it challenging to build and maintain the multidisciplinary workforce necessary to conduct investigations.
- The current uneven global distribution of the workforce leads to political and

[43]T. Tahsin et al., "Named Entity Linking of Geospatial and Host Metadata in GenBank for Advancing Biomedical Research," *Database* (2017): https://doi.org/10.1093/database/bax093. National Institutes of Health officials told us they have since made concerted efforts to increase collection and harmonization of sample collection location and date information. They also noted that in some cases, such data may be unavailable due to privacy or ethical concerns.

[44]The term "academic structure" is defined as the components of academic institutions and how they relate to each other. Components include academic careers, departments, plans, and subplans.

logistical challenges during a pandemic. For example, a 2021 study concluded that inadequate sequencing capacity because of limited skillsets, among other factors, hindered biosurveillance during the COVID-19 pandemic.[45]

- Some researchers told us that they faced criticism because of their involvement in investigating the origin of a pandemic, particularly when their conclusions were considered controversial. These researchers said they and others may be reluctant to participate in further investigations because of personal and professional risks.

We found that a national strategy could help to address these challenges. National strategies are "whole of nation" efforts that frequently include international components. They may be part of a structure of overlapping or supporting national strategies and typically involve sectors, organizations, entities, and resources outside the control of the federal government.[46]

[45]M. Dzobo et al., "Inadequate SARS-CoV-2 Genetic Sequencing Capacity in Zimbabwe: A Call to Urgently Address this Key Gap to Control Current and Future Waves," *IJID Regions*, vol. 1 (2021): ep. 3-4. https://doi.org/10.1016/j.ijregi.2021.09.004.

[46]See GAO, *Combating Terrorism: Evaluation of Selected Characteristics in National Strategies Related to Terrorism*, GAO-04-408T (Washington, D.C.: Feb. 3, 2004).

5 Selected Policy Options to Help Address Three Cross-Cutting Key Challenges for Investigating Pandemic Origin

Chapter 4 described three cross-cutting challenges that hinder researchers trying to investigate the origin of a pandemic:

- Lack of sufficient access to samples and genetic sequence data,
- Lack of standardized processes for genetic databases, and
- Lack of a sufficient and skilled interdisciplinary workforce.

GAO identified five policy options that may help address these challenges. These policy options are not mutually exclusive and represent possible actions that policymakers—who may include Congress, federal agencies, state and local governments, academic and research institutions, industry, and international organizations—could consider taking. Addressing the three broad challenges with these policy options could also help improve the ability of researchers to respond more quickly and effectively to potential future pandemics.

Policy Option: Federal policymakers and others could encourage international preparedness in advance of future outbreaks by supporting the development of multilateral agreements for accessing and sharing samples and genetic sequence data.

Challenge Addressed: Access to samples and genetic sequence data

Federal policymakers and others could help establish comprehensive multilateral, international agreements for accessing and sharing genetic sequence samples and data in advance of future outbreaks. These proactive agreements could include definitions of the roles and responsibilities of international investigation teams and incentives for adherence, helping ensure more timely access to critical information.

Potential implementation approaches

- Develop multilateral sample and data-sharing agreements—for example, to include expectations of timely access to samples and detailed standards for sample collection, sample storage, and metadata that countries will supply—as an objective in national pandemic origin investigation strategies.
- Work with international health organizations, such as the World Health Organization, to identify and address barriers to establishing multilateral, international agreements for ensuring access to genetic sequence samples and data, and support the development of such agreements.
- Seek agreement with stakeholders on incentives for participation, such as equitable access to vaccines and therapeutics. These incentives could also include economic assistance and assurances to mitigate stigmatization when promptly sharing samples and genetic sequence data.

Opportunities

- Ensuring timely access to genetic information and samples in the critical beginning stages of a pandemic as well as throughout an origin investigation may help in the determination of a pandemic's origin.
- Establishing standing agreements between nations before a pandemic occurs could assist in determination of a pandemic's origin.
- Incentives may help encourage reluctant countries to participate.

Considerations

- Countries may be unwilling to participate in such multilateral, international agreements because of concerns related to national sovereignty.
- Identifying an appropriate responsible entity to determine and monitor whether countries are following agreed-upon standard processes and their implementation may be time-consuming and challenging.[47]

Policy Option: Federal policymakers and others could empower or establish a working group to develop standardized processes for database use to support pandemic origin investigations.

Challenge Addressed: Lack of standardized processes for data submission, access, and use

A working group could develop standardized processes for submission of and access to data in databases such as GenBank.[48] Standardized processes could help ensure that all users submit and access the same kinds of data used for pandemic origin investigations.

Potential implementation approach

Federal policymakers and others—such as state and local policymakers, current database providers, developers, and users—could collaborate to identify and develop standardized processes for using genetic sequence databases. This could include updating documentation processes—such as clear instructions for types of sample metadata—for using GenBank and other databases and encouraging those database providers to implement these standardized processes.

[47]For example, it took 6 years for the Secretariat of the Convention on Biological Diversity's *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity* (an international agreement which aims at sharing the benefits arising from the use of genetic resources in a fair and equitable way) to develop and implement the agreement. However, the protocol still lacks a strong plan for compliance. The U.S. is not a signatory to the Nagoya Protocol or the Convention on Biological Diversity.

[48]Other databases may be operated by other countries or nongovernmental organizations.

Opportunities

- Developing standardized processes for databases could help ensure consistency of submitted data and metadata across multiple databases, improve researchers' access, and help researchers comprehensively compare genetic sequences. For example, standardized processes for recording geographic details of sample collections could help researchers who use the database examine information to better understand where a pathogen resides naturally.

- Implementing leading practices for genetic data integrity and associated metadata could help improve the quality of data in genetic sequence databases. For example, as discussed previously, we heard from researchers that some databases would only allow the researcher who entered a genetic sequence to change any of that information or to delete the sequence. Database governance practices that give database administrators a greater role in performing quality control could help ensure more data can be used to comprehensively compare genetic sequences to determine a pathogen's evolutionary ancestry and origin.

Considerations

- Standardized processes may be difficult to develop as there are risk-benefit trade-offs. For example, it is critical that access to certain novel pathogen sequences in databases be limited to trusted and credentialed individuals with a need to access those sequences. The working group would therefore need to balance the security of the databases with ensuring that researchers can access novel pathogen sequences, as needed, for critical work.
- Universities and industry researchers may have existing policies governing metadata to ensure privacy. For example, the benefits of including specific geographic information with biological samples must be weighed against any privacy concerns of the people and communities from which those samples were collected.
- It may be challenging for multiple stakeholders to agree on what data are important. For example, stakeholders may have different perspectives on what metadata should be required versus optional.

Policy Option: Policymakers could encourage the improvement of current, or development of new, genetic sequence database tools.

Challenge Addressed: Lack of standard user and application programming interfaces

Improving current genetic sequence database tools or developing new ones may help investigators determine a pandemic's origin more effectively. For example, redesigning current or creating new database user interfaces or APIs could help researchers perform genetic sequence comparisons more efficiently and aid in phylogenetic analyses.

Potential implementation approaches

- Policymakers could encourage improvements to sequence database tools—such as user interfaces or APIs—of current databases.
- Policymakers could incentivize—for example, via funding—the creation of new database user interfaces or APIs.

Opportunities

- Improved or new database user interfaces and APIs—as agreed upon by groups of end users and in conjunction with standard processes— could, for example, streamline researchers' data submission, access, and use and improve data quality.
- Improved or new database user interfaces and APIs could assist in addressing the projected future growth in genetic sequence data by, for example, enabling the analysis of large datasets stored in distributed cloud-based systems.[49]

Considerations

- Building new, or retooling current, database user interfaces and APIs could be time- and labor- intensive.
- It may be challenging for groups of users to agree on what database user interfaces and APIs features are important. For example, users may have different opinions on what is important to include in the user interfaces to make the databases more user-friendly or what applications need to communicate with the databases.

Policy Option: Policymakers could incentivize the development, retention, and growth of a workforce with the critical skills needed to conduct or support the work of characterizing the likely origin of a pandemic.

Challenge Addressed: Lack of a sufficient and skilled interdisciplinary workforce

Incentivizing the development of the workforce could increase the availability of skilled workers by creating international partnerships, among other things, and leveraging or creating training programs to encourage workforce growth and retention.

Potential implementation approaches

- Policymakers could encourage mechanisms to provide training, workforce development, and capacity building, including in areas considered hot spots of emerging infectious disease. Focusing on recruitment and consistent investment in global as well as domestic programs may increase the available workforce by increasing the number of skilled workers and retaining those workers.

[49]Additional technological needs to address the future growth in genetic sequence data may include data centers with fast, tiered storage systems, improved algorithms, data streaming approaches, and large-scale machine learning systems.

- Policymakers could leverage or enhance existing programs to provide incentives for students and research professionals to pursue careers in fields with skills necessary for pandemic origin investigations.

Opportunities

- Encouraging development of expertise in geographic areas where novel pathogens are likely to emerge would not only increase the overall global supply of skilled workers but also help to ensure the workforce is not concentrated in any one particular geographic region.
- Increased and improved educational initiatives could foster a generation of students and professionals with the multidisciplinary qualifications and skills needed to support pandemic origin investigations. For example, the National Science Foundation currently invests in numerous graduate student educational activities through a program that provides activities and training opportunities to augment students' research assistantships with non-academic research internships. Policymakers could continue to leverage or expand these types of programs by, for example, encouraging investment in multidisciplinary scientific fields that may support pandemic origin investigations.
- A sufficient and trained workforce skilled in origin investigations could contribute to other areas such as public health, biotechnology, infectious diseases, or other types of related biological research and development.

Considerations

- Pandemic origin investigations tend to be episodic and irregular. As a result, it may be difficult to adequately plan for and consistently fund staffing in science fields related to pandemic investigations.
- The scientific community may resist any alteration to current academic structures, and it may be challenging to adapt priorities, processes, and funding in a sufficiently timely manner needed to respond to a pandemic. As a result, attracting qualified people into the necessary workforce fields may be challenging if those fields are marginalized and underfunded.
- Researchers may experience unwanted attention, pressure, harassment, or influence because of their involvement in pandemic origin investigations. As a result, increasing the size of the workforce may not lead to sustained expertise if experienced researchers leave the field or refuse to participate in pandemic origin investigations.

Policy Option: Federal policymakers could augment or develop a national strategy to better coordinate and collaborate domestically and internationally on pandemic origin investigations.

Challenges Addressed: All

The 2022 National Biodefense Strategy and Implementation Plan may assist in addressing the cross-cutting challenges we identified. For example, the 2022 Strategy includes an Early Warning priority area that encompasses targets and corresponding

actions related to determining the origin of biological events, including infectious disease outbreaks.[50] However, the 2022 Strategy does not specifically outline how the lead and support departments and agencies will coordinate and collaborate to address origin determination. Augmenting the 2022 Strategy or developing a separate strategy with these specifics could better position the nation to play a leading role in pandemic origin investigations.

Potential implementation approaches

- Federal policymakers could augment the National Biodefense Strategy to specify how lead and support departments and agencies will coordinate and collaborate with domestic and international partners to address pandemic origin investigations.
- Federal policymakers could develop a new, standalone, national strategy focused on pandemic origin investigations that describes how federal entities will coordinate and collaborate with domestic and international partners on such investigations.

Opportunities

- A national strategy could help address the challenges that hinder pandemic origin investigations.
- Federal coordination and collaboration leadership, guided by a national strategy, could increase preparedness for future pandemic origin investigations.
- Understanding pandemic origins could help mitigate health and economic costs associated with pandemics by, for example, facilitating surveillance that could identify future pandemics more quickly.
- A national strategy that includes pandemic origin investigations could help identify and quickly deploy resources needed for timely investigation of a pandemic's origin.

Considerations

- Allocating resources and defining how federal agencies and others will collaborate may be challenging because of the number and types of entities with relevant expertise that would be involved.
- During nonpandemic periods, other priorities and needs may arise and make it challenging to provide sustained resources and support

[50]This priority area includes characterizing biological material to support investigations, origin determination, and attribution as well as supporting United Nations investigations of outbreaks of unknown origin. See Office of Science and Technology Policy, *National Biodefense Strategy and Implementation Plan for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security* (Washington, D.C.: October 2022).

needed for maintaining a national strategy.

- Augmenting or developing a new strategy would require careful consideration to avoid duplication, overlap, or fragmentation with existing related strategies, such as those for biodefense.
- Integrating a goal of pandemic origin investigations into existing strategies could dilute the focus and resources of the existing strategies.

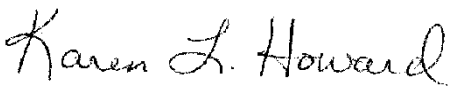
6 Agency and Expert Comments

We provided a draft of this product to the Department of State, Department of Defense, Department of Homeland Security, Department of Energy's Office of Science and National Nuclear Security Administration Laboratories, Office of the Director of National Security's Intelligence Advanced Research Projects Activity, Office of Science and Technology Policy, Department of Health and Human Services' Centers for Disease Control and Prevention and National Institutes of Health, Department of Justice's Federal Bureau of Investigation, National Institute of Standards and Technology, National Science Foundation, and United States Agency for International Development for review. Six agencies provided technical comments on the draft report, which we incorporated as appropriate.

We also invited the participants from our expert meeting to review our draft report. Of the 27 experts, 17 agreed to receive the draft for review and 10 provided technical comments. We incorporated their technical comments as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 5 days from the report date. At that time, we will send copies of this report to the appropriate congressional committees and other interested parties. In addition, the report is available at no charge on the GAO website at https://www.gao.gov.

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



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

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Committee on Energy and Commerce
House of Representatives

The Honorable Bob Latta
Chair
Subcommittee on Communications and Technology
Committee on Energy and Commerce
House of Representatives

The Honorable Jeff Duncan
Chair
Subcommittee on Energy, Climate, and Grid Security
Committee on Energy and Commerce
House of Representatives

The Honorable Bill Johnson
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The Honorable Earl L. "Buddy" Carter
House of Representatives

The Honorable Dan Crenshaw
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The Honorable John Curtis
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The Honorable Richard Hudson
House of Representatives

The Honorable John Joyce, MD
House of Representatives

The Honorable Debbie Lesko
House of Representatives

The Honorable Gary Palmer
House of Representatives

The Honorable Greg Pence
House of Representatives

The Honorable Steve Scalise
House of Representatives

The Honorable Tim Walberg
House of Representatives

Appendix I: Objectives, Scope, and Methodology

Objectives

This report identifies and discusses:

1. key technologies available for pandemic origin investigations;
2. strengths and limitations of these tools and how researchers use them to investigate pandemic origins;
3. cross-cutting challenges researchers face in trying to determine a pandemic's origin; and
4. policy options that may help address the limitations and cross-cutting challenges of using these key technologies to determine the origin of a pandemic.

Scope and methodology

To address our first three objectives, we assessed available and developing technologies and approaches that are currently used in pandemic origin investigations. For all of our objectives we reviewed peer-reviewed scientific literature and other documents describing current and developing tools, including reports from the Centers for Disease Control and Prevention, Office of the Director of National Intelligence, the Johns Hopkins Center for Health Security, World Health Organization, and select national laboratories; interviewed federal agency officials and experts from government, academia, industry, and the nonprofit sector; and convened a 3-day expert meeting with assistance from the National Academies of Sciences, Engineering, and Medicine to discuss the objective topics. We also reviewed federal agency guidance on the development and deployment of these technologies for pandemic origin investigations.

Limitations to scope

The list of key technologies for pandemic origin investigations discussed in this report is not intended to be exhaustive. Based on our review of the literature and discussions with federal agency officials and other experts, we selected technologies currently in use or under development by researchers to investigate a pandemic's origin. We did not include all possible types of pathogens; we focused on those that are likely to lead to direct human-human transmission. For example, we did not include pathogens that cause foodborne outbreaks. We also did not review or include classified data or intelligence. Since pandemics pose a global threat, the policy options we identified represent possible actions U.S. policymakers and international stakeholders could take.

Literature search

In the course of our review, we worked with a GAO research librarian to conduct a literature search of key technologies for identifying and characterizing pandemic pathogens.[51] The librarian conducted literature searches with

[51]For the purposes of this report, the term "technologies" includes the instruments, techniques, skills, methods, and processes used in pathogen characterization.

Scopus using search terms including "pandemic origins," "biosurveillance," "SARS-CoV-2," and "bioinformatics," among other keywords relevant to technologies for characterizing pathogens. We conducted a broad search of materials published within the last 10 years, including scholarly articles and government reports. From these searches, we identified and selected relevant articles to include in our review. We used the results of our literature review to inform our findings as well as identify experts to interview or invite to participate in our expert meeting.

Interviews

We interviewed federal agency officials and researchers as well as nonfederal experts with a diverse set of perspectives on the science and application of these technologies. These experts included individuals from 11 relevant federal agencies: the Department of State, Department of Defense, Department of Homeland Security, Department of Energy's Office of Science and National Nuclear Security Administration Laboratories, Office of the Director of National Security's Intelligence Advanced Research Projects Activity, Office of Science and Technology Policy, Department of Health and Human Services' Centers for Disease Control and Prevention and National Institutes of Health, Department of Justice's Federal Bureau of Investigation, National Institute of Standards and Technology, National Science Foundation, and United States Agency for International Development. We also interviewed experts from technology companies, universities, and research institutes that use or develop genome sequencing, proteomics technologies, and laboratory characterization methods for pathogen characterization; representatives from national and international health organizations (e.g., the Association of Public Health Laboratories, Association of State and Territorial Health Officials, EcoHealth Alliance, and World Health Organization); and other individuals with expertise with technologies used for pandemic origin investigations.

Expert meeting

To address all of our objectives, we also held an expert meeting March 22-24, 2022. This meeting was held with assistance from the National Academies of Sciences, Engineering, and Medicine and was divided into six sessions: (1) genomic technologies for determining pathogen sequences; (2) genomic technologies for characterizing pathogen sequences to inform origin; (3) genomic technologies for determining analytical confidence and reproducibility; (4) non-genomic technologies for characterizing pathogens; (5) surveillance technologies that would inform pandemic pathogen origin; and (6) potential policy options that could help address technology limitations and other challenges.[52]

We selected meeting participants based on their expertise in at least one area related to our four objectives. We provided the National

[52]This meeting of experts was planned and convened with assistance from the National Academies of Sciences, Engineering, and Medicine to better ensure that a breadth of expertise was brought to bear in its preparation. However, all final decisions regarding meeting substance and expert participation are the responsibility of GAO.

Academies of Sciences, Engineering, and Medicine with descriptions of the expertise needed by expert meeting participants. From this information, the National Academies of Sciences, Engineering, and Medicine provided an initial list of potential participants for the expert meeting. We reviewed the list and provided an additional list of experts based on our review of the literature.

In addition to evaluating experts on the basis of their expertise, we evaluated them for any conflicts of interest. A conflict of interest was considered to be any current financial or other interest, such as an organizational position, that might conflict with the service of an individual because it could (1) impair objectivity or (2) create an unfair competitive advantage for any person or organization. Of the 27 experts who participated in the expert meeting, some were affiliated with companies, government, or research-funding entities. We took these affiliations into consideration as potential conflicts of interest when conducting our analysis and preparing our report. We determined that these experts' affiliations were unlikely to bias our overall reporting.

Policy options

Based on our research, we developed a series of policy options. Policy options are not formal recommendations for federal agencies, or matters for congressional consideration, but they are intended to represent possible options policymakers can take to address a policy objective. For each policy option, we discussed potential opportunities and considerations. These are not listed in any particular order, nor are they inclusive of all possible policy options. Based on the goal of improving U.S. pandemic preparedness, we decided on an objective designed to identify options that could help improve capabilities for pandemic origin investigations. We limited policy options to those that fit the objective and fell within the report scope.

To develop our policy options, we compiled a list of possible options over the course of our work based on review of the literature, interviews with experts, and our expert meeting held March 22–24, 2022. We further refined and assessed these options to ensure they were adequately supported by the evidence we collected, could be feasibly implemented, and fit into the overall scope of our work. We then analyzed the information we collected to identify potential benefits and considerations of implementing each policy option. The policy options and analyses were supported by documentary and testimonial evidence.

We conducted our work from August 2021 to January 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. Consistent with our quality assurance framework, we provided the relevant agencies and experts with a draft of our report and solicited their feedback, which we incorporated as appropriate. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

Appendix II: Expert Participation

We convened a 3-day meeting of 27 experts with assistance from the National Academies of Sciences, Engineering, and Medicine to inform our work on technologies for determining pandemic origin; the meeting was held virtually March 22–24, 2022. The experts who participated in this meeting are listed below. Some of these experts gave us additional assistance throughout our work, including four experts who provided additional assistance during our study by sending material for review or participating in interviews and 10 experts who reviewed our draft report for accuracy and provided technical comments.

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Associate Director

Penn State Animal Diagnostic Laboratory (ADL)

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NIH-funded Physician/Scientist, Division of Infectious Disease

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Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard

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(105406)

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United States Government Accountability Office

Report to Congressional Committees

January 2023

PUBLIC HEALTH PREPAREDNESS

HHS Could Improve Oversight of Research Involving Enhanced Potential Pandemic Pathogens

GAO-23-105455

GAO Highlights

Highlights of GAO-23-105455, a report to congressional committees

January 2023

PUBLIC HEALTH PREPAREDNESS

HHS Could Improve Oversight of Research Involving Enhanced Potential Pandemic Pathogens

Why GAO Did This Study

Research involving pandemic pathogens is crucial to ensure the nation's ability to prepare for, respond to, and recover from public health threats. For example, such research resulted in COVID-19 vaccines and therapeutics to prevent severe disease or death. However, a number of incidents and research projects—including research that enhanced the transmissibility of influenza between mammals—have raised questions about the adequacy of HHS oversight of the safety of such research.

The CARES Act includes a provision for GAO to report on ongoing federal efforts to prepare for, respond to, and recover from COVID-19. This report examines the extent to which HHS's oversight Framework for enhanced potential pandemic pathogen research is effective; and gaps that exist in HHS's broader oversight of such research, among other things.

GAO reviewed HHS's oversight policies and programs as well as documentation for selected research grants. GAO also assessed the Framework against GAO's elements of effective oversight. GAO interviewed HHS officials and select subject matter experts from the research biosafety and biosecurity community.

What GAO Recommends

GAO is making three recommendations to improve HHS's oversight of research, including developing and documenting a standard for "reasonably anticipated" and assessing the risk of statutory limitations. HHS neither agreed nor disagreed with two of the recommendations and agreed with the third.

View GAO-23-105455. For more information, contact Mary Denigan-Macauley at (202) 512-7114 or DeniganMacauleyM@gao.gov.

What GAO Found

The Department of Health and Human Services (HHS) oversees high-risk research involving potential pandemic pathogens, which are defined as likely highly transmissible and virulent, and capable of causing significant morbidity or mortality. SARS-CoV-2, which causes COVID-19 disease, is an example of a pandemic pathogen. In 2017, HHS developed an oversight policy (the Framework) that requires funding agencies to refer proposed research that is "reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens" to the Department for an additional review of associated risks and benefits, among other things.

Researcher conducting high-risk research

Source: Centers for Disease Control and Prevention. | GAO-23-105455

GAO found that HHS's Framework does not fully meet the key elements of effective oversight identified in past work. For example, the Framework does not provide a standard to help funding agencies interpret what "reasonably anticipated" means. Until HHS develops and documents such a standard, the Framework allows for subjective and potentially inconsistent interpretations of the requirement—leaving HHS without assurance the department is reviewing all necessary research proposals.

HHS also oversees research involving certain pandemic pathogens through its Federal Select Agent Program—a list-based program regulating the possession, use, and transfer of certain pathogens. However, HHS faces trade-offs in adding newly emerged pathogens, like SARS-CoV-2, to the list because, as officials told GAO, doing so would impede the public health response by burdening diagnostic and treatment facilities with additional reporting and inspection requirements. The statute authorizing the Federal Select Agent Program limits HHS's ability to waive or postpone these requirements during public health emergencies for a maximum of 60 days. HHS has not assessed the risk this limitation poses to its oversight of known pandemic pathogens. Until the risk of this statutory limitation is assessed and action taken to mitigate any risks, HHS will continue to face tradeoffs between impeding public health response efforts and allowing high-risk research involving known pandemic pathogens to be conducted without appropriate HHS oversight.

Contents

Abbreviations

ASPR	Administration for Strategic Preparedness and Response
CDC	Centers for Disease Control and Prevention
DSAT	Division of Select Agents and Toxins
DURC	Dual Use Research of Concern
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NSABB	National Science Advisory Board for Biosecurity
OSTP	Office of Science and Technology Policy
SARS	Severe Acute Respiratory Syndrome

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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January 18, 2023

Congressional Committees

High-risk life science research has been a topic of interest in recent congressional hearings.[1] High-risk research that results in the acquisition of new or enhanced biological characteristics in microorganisms is of particular concern, as it can involve enhancing the transmissibility or virulence of pathogens.[2] By enhancing these features, this research typically aims to improve understanding of pathogens, their interactions with human hosts, and their pandemic potential. It can be used to better inform public health and preparedness efforts and develop medical countermeasures. For example, this type of research led to the development of influenza vaccines.

Oversight to ensure the biosafety and biosecurity of pandemic pathogens is a responsibility shared across multiple departments. Generally, the Department of Health and Human Services (HHS) and its component agencies—including the Administration for Strategic Preparedness and Response (ASPR),[3] the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Centers for Disease Control and

[1]See *Revisiting Gain of Function Research: What the Pandemic Taught Us and Where Do We Go From Here? Hearing before the Subcomm. on Emerging Threats and Spending Oversight of the S. Comm. on Homeland Security and Governmental Affairs*, 117th Cong., (2022).

Life sciences covers all sciences relating to living organisms, encompassing biology, biotechnology, genomics, pharmaceutical and biomedical research and techniques.

[2]National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation And Oversight Of Proposed Gain-Of-Function Research*, May 2016.

[3]On July 22, 2022, HHS designated ASPR, which was formerly the Office of the Assistant Secretary for Preparedness and Response, as a stand-alone agency within the Department and announced that ASPR's name changed to the Administration for Strategic Preparedness and Response. According to HHS, the change will allow ASPR to mobilize a coordinated national response to future disasters and emergencies more effectively and efficiently.

Prevention (CDC)—are most directly involved in leading public health preparedness and response efforts, and associated research.[4]

Over the last 10 years, a number of incidents have led to questions about the nature and adequacy of U.S. government oversight of pathogens with pandemic potential and laboratory safety more generally. Such incidents included HHS-funded research in 2012 that involved the manipulation of avian influenza viruses to create human pathogens with pandemic potential, as well as unrelated laboratory safety lapses that could have released dangerous pathogens.[5]

In 2017, HHS instituted a new oversight framework for HHS-funded enhanced potential pandemic pathogen research (hereafter referred to as the Framework). The Framework defines a potential pandemic pathogen as being "likely highly transmissible and likely capable of wide and uncontrollable spread in human populations" and "likely highly virulent and likely to cause significant morbidity and/or mortality in humans." It further defines an enhanced potential pandemic pathogen as one resulting from the enhancement of the transmissibility and/or virulence of a pathogen.[6] This new Framework was developed in response to guidance from the White House Office of Science and Technology Policy (OSTP) recommending federal departments adopt a department-level

[4]Several federal departments and agencies share biodefense responsibilities to assess, prevent, and respond to biological threats. In these efforts, HHS coordinates with the Department of Homeland Security, the Department of Defense, and the Department of Agriculture among others on biosafety.

[5]Concerns about the risks of this type of research, which may be referred to as gain of function, were heightened after the publication of two separate experiments in 2012 that demonstrated how highly pathogenic avian influenza—an influenza strain that has increased ability to cause disease and mortality in birds—could be manipulated in the lab to produce genetic mutations that allowed the virus to become transmissible between mammals. In addition, concerns about laboratory safety and biosecurity were renewed in light of serious safety lapses at federal laboratories. For instance, in June 2014, CDC staff inadvertently transferred live *Bacillus anthracis* bacteria—which they erroneously believed had been inactivated by an experimental procedure—to a different laboratory, resulting in the potential exposure of many workers to a highly virulent strain of the pathogen that causes anthrax disease. In July 2014, FDA researchers discovered that vials of viable smallpox virus had been left in the cold room of an FDA laboratory instead of in appropriately secure repositories. See GAO, *High Containment Laboratories: Recent Incidents of Biosafety Lapses,* GAO-14-785T (Washington, D.C.: July 16, 2014) for more information.

[6]Enhanced potential pandemic pathogens do not include naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential.

pre-funding review mechanism for federally funded research that is anticipated to create, transfer, or use enhanced pathogens with pandemic potential.[7] White House OSTP works with the White House National Security Council to coordinate policy across the federal government.

The CARES Act includes a provision for GAO to conduct and report on its monitoring and oversight of activities and funds to prepare for, respond to, and recover from COVID-19.[8] This report focuses on HHS's oversight of research with potential pandemic pathogens, which HHS funds to assess the pandemic potential of emerging infectious agents such as viruses, and to inform public health and preparedness efforts. Specifically, in this report, we

1. describe how HHS uses its Framework and other programs to oversee federally funded research involving enhanced potential pandemic pathogens;
2. assess the extent to which HHS's Framework has the elements of effective oversight;
3. examine what gaps exist in HHS's broader oversight of research involving enhanced potential pandemic pathogens; and
4. assess the extent to which HHS oversees privately funded research.

To describe how HHS uses its Framework and other programs to oversee federally funded research involving enhanced potential pandemic pathogens, we reviewed federal regulations, guidance, and policies that HHS and its agencies use to oversee this research. In particular, we focused on how HHS and its agencies oversee the biosafety and biosecurity of this research. Biosafety includes the practices and equipment that ensure that lab workers, the community, and the environment are protected from infectious pathogens and biological hazards. Biosecurity includes the practices to ensure the protection and control of biological materials in laboratories to protect them from theft, loss, or misuse. We interviewed HHS officials, including those from NIH, CDC, and FDA about how they conduct and coordinate oversight.

[7]Office of Science and Technology Policy, *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)*, (Washington, D.C.: Jan. 2017).

[8]Pub. L. No. 116-136, § 19010(b), 134 Stat. 281, 580 (2020). All of GAO's reports related to the COVID-19 pandemic are available on GAO's website at https://www.gao.gov/coronavirus.

To examine the extent to which HHS's oversight of enhanced potential pandemic pathogen research has elements of effective oversight, we assessed HHS's policies, agency guidance, and other documentation against GAO's key elements of effective oversight. GAO identified five key elements of effective oversight in prior work in areas where low-probability adverse events can have significant and far-reaching effects. For example, we have applied these elements in assessing federal oversight of nuclear safety, oil and gas management, and high-containment laboratories.[9] These elements are:

- **Ability to Perform Reviews.** The organization conducting oversight should have the ability to perform reviews, including the working knowledge necessary to review compliance with requirements.
- **Transparency.** The organization conducting oversight should provide access to key information, as applicable, to those most affected by operations.
- **Technical Expertise.** The organization conducting oversight should have sufficient staff with the expertise to perform sound safety and security assessments.
- **Independence.** The organization conducting oversight should be structurally distinct and separate from the entities it oversees.
- **Enforcement Authorit**y. The organization conducting oversight should have clear and sufficient authority to require that entities achieve compliance with requirements.

We also obtained and reviewed documentation for the two awards that involved enhancement of potential pandemic pathogens to make them more transmissible and that were reviewed under the Framework. We reviewed the documentation to examine how HHS oversaw the biosafety and biosecurity of the research. Additionally, we interviewed 10 subject matter experts, comprising nine individual researchers, academics, scientific advisory board members, and one organization representing biosafety officers. These subject matter experts were selected because of their roles as current or former members of National Science Advisory Board for Biosecurity (NSABB)—a federal advisory committee that addresses issues related to biosecurity and dual use research—

[9]See GAO, *High Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogen*s, GAO-18-145 (Washington, D.C.: Oct. 19, 2017).

membership in the Association for Biosafety and Biosecurity, or authorship of recently published academic articles related to the enhancement of potential pandemic pathogens.[10] We interviewed these experts about identified and potential risks of research with potential pandemic pathogens. We accessed and reviewed the recorded webcast of NSABB meetings and stakeholder engagement meetings to obtain perspectives from other members of the research biosafety and biosecurity community.[11]

To identify any gaps that exist in HHS's oversight of research involving enhanced potential pandemic pathogens, we reviewed federal regulations, guidance, and policies that HHS and its agencies use to oversee this research to identify their scope and applicability. In evaluating this information, we compared policies and procedures against federal internal control standards related to assessing and managing risk.[12] We also obtained and reviewed publicly available documentation on a research grant that involved studying potential pandemic pathogens rather than enhancing the pathogens' functions and, thus, did not fall within HHS's oversight of research involving potential pandemic pathogens. We reviewed the documentation to examine how NIH identified risks and oversaw the biosafety and biosecurity of the research. We interviewed HHS and agency officials from NIH and CDC about how they conduct and coordinate their oversight. We interviewed officials from OSTP and the National Security Council about broader federal oversight in this area. We also interviewed subject matter experts described above to obtain their perspective on federal oversight of high-risk research.

[10]Selected experts came from a broad range of academic and industry backgrounds representing disciplines such as epidemiology, veterinary medicine, microbiology, immunology, biosafety, and biosecurity. Our findings from interviews with these experts are not generalizable to the entire spectrum of biological research experts.

[11]NIH held stakeholder engagement meetings on April 27, 2022, and June 29, 2022, to gather feedback to help inform evaluations of the Framework and dual use research of concern (DURC) policies, respectively. These sessions were recorded and available for view on NIH's website: (April Session) https://videocast.nih.gov/watch=45230; (June session) https://videocast.nih.gov/watch=45698. NIH held a meeting on September 21, 2022, to share NSABB's preliminary findings and recommendations for public input. That session was recorded and available for view on https://videocast.nih.gov/watch=46218.

[12]GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: Sept. 10, 2014). Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

To assess the extent to which HHS oversees privately funded research, we reviewed federal regulations, guidance, and policies governing research biosafety and biosecurity and examined their scope and applicability. In evaluating this information, we compared policies and procedures against the federal internal control standards related to using quality information and managing risk. We also reviewed past GAO work on this topic.[13] We interviewed HHS and agency officials as well as officials from the White House OSTP and the National Security Council about federal oversight for privately funded research.

We conducted this performance audit from September 2021 to January 2023 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

HHS leads the federal public health and medical response to potential biological threats and emerging infectious diseases. Within HHS, ASPR coordinates HHS policy development in research biosafety and biosecurity in collaboration with other departmental, agency, and outside experts.[14] Other HHS agencies—including NIH, CDC, and FDA—conduct their own research—known as intramural research—to identify and prepare for public health threats. They also review, provide guidance, and fund research conducted by others—known as extramural research—that may involve public health risks. This extramural research is typically conducted at universities, medical schools, private biotechnology companies, and other research institutions. For example, HHS—including NIH, and FDA—in partnership with the Department of Defense, implemented Operation Warp Speed, which provided financial support and oversight of nonfederal partners to accelerate the development of

[13]GAO, *High-Containment Laboratories: National Strategy for Oversight is Needed.* GAO-09-574 (Washington, D.C.: Sept. 21, 2009).

[14]ASPR leads the HHS Biosafety and Biosecurity Coordinating Council, an intradepartmental group established by the HHS Immediate Office of Secretary, to provide a mechanism to share best practices, enhance visibility across HHS agencies, and coordinate biosafety and biosecurity policy development as well as oversight activities. The HHS Biosafety and Biosecurity Coordinating Council includes members from CDC and NIH, among others.

COVID-19 vaccines and therapeutics to prevent severe disease and death.[15]

Funding agencies are responsible for conducting ongoing oversight of research through monitoring compliance with the terms and conditions of the award. NIH is the primary federal agency that conducts and supports biomedical research, and provides oversight in a variety of ways:[16]

- As a funding agency, NIH manages and administers federal awards to ensure that federal funding is expended, and associated programs are implemented in accordance with statutory and other grant requirements. To do so, NIH monitors grantee performance and use of NIH funds.[17] In addition to its standard grants policy, NIH may incorporate specific terms and conditions reflecting the specific risks of the research. For example, NIH requires grantees to provide periodic progress reports describing research findings, and NIH may add biosafety terms to subsequent grant awards based on those reports.[18]
- NIH also provides biosafety and biosecurity guidance. For example, NIH, in conjunction with CDC, develops and disseminates *Biosafety in*

[15]GAO, *COVID-19: Federal Efforts Accelerate Vaccine and Therapeutic Development, but More Transparency Needed on Emergency Use Authorizations,* GAO-21-207 (Washington, D.C.: Nov. 17, 2020).

[16]According to NIH, approximately 95 percent of NIH budget goes to support research. This includes grants and subawards to support research conducted outside the United States. CDC and FDA also fund research, with 5 percent of CDC's funding supporting research grants. FDA did not provide information about the percentage of agency funding dedicated to supporting research grants.

[17]Grantees must monitor the activities of subrecipients, including foreign subrecipients, to ensure that subawards are used for authorized purposes in compliance with relevant laws and the terms and conditions of the subaward.

[18]The Policy Statement requires that grantees report at least annually on budget information, but NIH has the flexibility to specify the elements for reporting and require more frequent reporting. The grant terms and conditions include requirements for the content and frequency of the progress reports. Progress reports include sections to report whether the major goals of the research have changed, accomplishments toward those goals, and plans for the next reporting period to accomplish the research goals.

Microbiological and Biomedical Laboratories, an advisory document recommending best biosafety practices to researchers.[19]

NIH comprises 27 institutes and centers. These institutes and centers both conduct and support biomedical research specific to their unique missions, which generally focus on a specific disease (e.g., cancer), a particular organ (e.g., eye), or a stage in life (e.g., childhood). NIH's National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research aimed at understanding, treating, and ultimately preventing the spread of infectious diseases. Among the institutes, NIAID has a unique mandate that requires it to respond to emerging public health threats, including emerging and re-emerging infectious diseases (such as COVID-19 and mpox, respectively).[20] Among the institutes, NIAID is most directly involved in supporting or conducting research with potential pandemic pathogens.

In addition to oversight through grant review, some research involving pathogens that have the potential to pose a severe threat to human health—such as the Ebola and mpox viruses—is considered to pose higher risk to public health and safety, and may also be subject to other oversight governing the use of these pathogens.

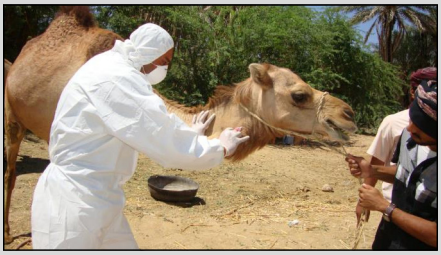
[19]NIH also developed and administers the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*). These guidelines detail safety practices and containment procedures for research involving manipulated or laboratory-created nucleic acid molecules (i.e., genetic building blocks) including the creation and use of organisms and viruses containing these molecules. In addition to providing biosafety guidance for a broad array of work with nucleic acids, the *NIH Guidelines* are a term and condition of NIH funding and they require researchers and institutions receiving NIH funds to obtain prior approval from the NIH director for any work involving the deliberate transfer of drug resistance traits to bacteria.

[20]Mpox was formerly known as monkeypox. The World Health Organization recommended the name change in November 2022.

Viruses Subject to the Federal Research Funding Pause between 2014-2017

Influenza Virus: In 2009, the most recent influenza pandemic, primarily affected children and young adults and led to over 12,000 deaths in the United States.

MERS-CoV: Has been found in camels and was first reported in Saudi Arabia in 2012. It has since spread to 27 countries, including the United States and led to 894 deaths as of July 2022. Most people infected with MERS developed fever, cough, and shortness of breath. MERS fatality rate is approximately 35 percent.



A veterinarian extracts blood samples from a camel's neck.

SARS-CoV: A viral respiratory illness first reported in Asia in February 2003. It spread to 29 countries, infecting over 8,000 people and resulting in over 770 deaths. SARS case fatality rate is approximately 10 percent. Since 2004, no SARS cases have been reported.

A health provider in the process of acquiring information from a SARS patient in a clinical setting.

Source: The Centers for Disease Control and Prevention (CDC) (information, photos), World Health Organization (information). | GAO-23-105455

In the fall of 2014, the U.S. government paused funding for a specific type of high-risk research that results in the acquisition of new or enhanced biological characteristics in microorganisms—referred to as gain-of-function research. Specifically, the U.S. government paused funding for gain-of-function research that was anticipated to enhance the transmissibility or pathogenicity of influenza viruses, Middle East Respiratory Syndrome, and Severe Acute Respiratory Syndrome (SARS) coronaviruses.[21] At the same time, the U.S. government embarked on a process to re-evaluate the risks and benefits of gain-of-function research and to develop policies to govern the funding and oversight of such research. During this time, the U.S. government sought input from the NSABB and other stakeholders on the risks and benefits of research involving potential pandemic pathogens, as well as recommendations for strengthening oversight.

In 2016, NSABB found that a small subset of gain-of-function research entails risks that were potentially significant enough to warrant additional oversight, and recommended that such research be subjected to additional review and oversight. Specifically, NSABB recommended the federal government take the following actions:

1. develop an additional, multidisciplinary review for any gain-of-function research that could generate a pathogen that is: a) highly transmissible and likely capable of wide and uncontrollable spread in human populations; and b) highly virulent and likely to cause significant morbidity and/or mortality in humans prior to determining whether such research is acceptable for funding. If funded, such projects should be subject to ongoing oversight at the federal and institutional levels;
2. utilize an advisory body designed for transparency and public engagement as part of the U.S. government's ongoing evaluation of oversight policies for gain-of-function research of concern;
3. consider ways to ensure that gain-of-function research of concern conducted within the United States or by U.S. companies be subject to oversight, regardless of funding source.[22]

[21]See https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research accessed August 24, 2021. The National Institutes of Health (NIH) identified 21 projects or awards that contained experiments that were subject to the research funding pause.

[22]National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation And Oversight Of Proposed Gain-Of-Function Research*, May 2016.

HHS's Framework and Other Programs for Overseeing Federally Funded Enhanced Potential Pandemic Pathogen Research

Potential and Enhanced Potential Pandemic Pathogens

The U.S. Department of Health and Human Services defines a potential pandemic pathogen as being "likely highly transmissible and likely capable of wide and uncontrollable spread in human populations" and "likely highly virulent and likely to cause significant morbidity and/or mortality in humans."

It further defines an enhanced potential pandemic pathogen as one resulting from the enhancement of the transmissibility and/or virulence of a pathogen.

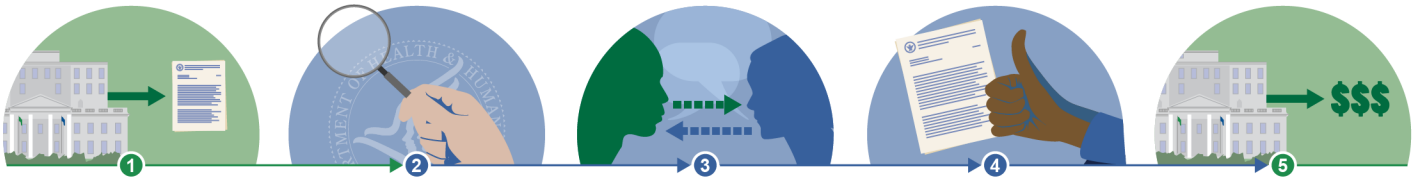
Source: HHS. | GAO-23-105455

HHS's 2017 Framework establishes a departmental-level review process for research proposals that are submitted for HHS funding and involve enhanced potential pandemic pathogens. According to the Framework, this includes research proposals to enhance the transmissibility or virulence of pathogens that already have the likely potential to cause wide and uncontrollable disease, resulting in significant morbidity and mortality in human populations.

The Framework's definition of an enhanced potential pandemic pathogen specifically excludes naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential. The Framework also excludes projects that consist of surveillance activities,
including sampling and sequencing of pathogens, and activities associated with developing and producing vaccines, such as generating virus strains that replicate quickly (for an example of the research excluded under the Framework, see app. II).

The departmental-level review is layered onto a funding agency's standard grant review process and provides non-binding recommendations for the funding agency to consider in deciding whether to fund a research grant proposal (see fig. 1).

Figure 1: Department of Health and Human Services (HHS) Process for Reviewing Research Considered for Funding That Involves Enhanced Potential Pandemic Pathogens



1. Funding agency staff identify research proposals that are reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens and refer them for departmental review.
2. A multidisciplinary departmental review group applies criteria to critically evaluate the risks and benefits of the proposed research.
3. The departmental review group provides funding agency interim feedback and comments on, for example, researchers' proposed methodology or risk mitigation measures. Funding agency responds.
4. Once a satisfactory conclusion is reached on the interim feedback, the departmental review group makes nonbinding recommendations on HHS funding, including suggestions for additional risk mitigation measures.
5. Funding agency decides whether to fund research and may incorporate the departmental review group's recommendations into grant terms and conditions. Funding agency monitors funded research under standard grant oversight processes.

Source: GAO analysis of HHS documentation. | GAO-23-105455

Department of Health and Human Services (HHS) Review Criteria for Assessing Certain High-Risk Research Proposals

- The research has been evaluated by an independent expert review process (whether internal or external) and has been determined to be scientifically sound.
- The pathogen that is anticipated to be created, transferred, or used by the research must be reasonably judged to be a credible source of a potential future human pandemic.
- An assessment of the overall potential risks and benefits associated with the research determines that the potential risks as compared to the potential benefits to society are justified.
- There are no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk than does the proposed approach.
- The investigator and the institution where the research would be carried out have the demonstrated capacity and commitment to conduct it safely and securely, and have the ability to respond rapidly, mitigate potential risks and take corrective actions in response to laboratory accidents, lapses in protocol and procedures, and potential security breaches.
- The research's results are anticipated to be responsibly communicated, in compliance with applicable laws, regulations, and policies, and any terms and conditions of funding, in order to realize their potential benefit.
- The research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing federal and institutional oversight of all aspects of the research throughout the course of the research.
- The research is ethically justifiable. Non-maleficence, beneficence, justice, respect for persons, scientific freedom, and responsible stewardship are among the ethical values that should be considered by a multidisciplinary review process in making decisions about whether to fund research involving potential pandemic pathogens.

Source: HHS. | GAO-23-105455

Specifically, under the Framework, HHS funding agencies are to conduct a review of research proposals that are being considered for federal funding to identify research proposals that are reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens. If the funding agency determines that the research fits the scope, the funding agency then refers such research proposals to a multi-disciplinary departmental review group, coordinated by ASPR, to assess the risks, benefits, and the researchers' capacity to ensure biosafety. According to the Framework, a multidisciplinary departmental review will be conducted in order to guide HHS funding decisions, and it will be based upon the identified criteria.

After its review, the departmental review group makes a nonbinding recommendation to the relevant HHS funding agency, which the agency considers in deciding whether to fund the research or impose additional risk-mitigation measures as a condition of funding the research. If the funding agency moves forward with funding the research proposal, the funding agency is responsible for incorporating any additional requirements into the grant and conducting oversight to ensure compliance through its standard grant oversight responsibilities. The funding agency must report its decision to the departmental review group and OSTP. ASPR officials told us they may require that funding agencies notify ASPR if the approved research results in unexpected outcomes.

Since the Framework's implementation in 2017, HHS has reviewed three research proposal submissions, all referred by NIH as of September

2022.[23] Of these three proposals, NIH adopted the departmental group recommendation for two of the studies. Both studies involved highly pathogenic avian influenza viruses—influenza strains that have increased ability to cause disease and mortality in avian species—and both have since concluded.[24] The third proposal, also involving influenza, was determined to be acceptable for funding with additional risk mitigation measures by the departmental review group. According to NIH, the agency decided to fund the proposal after the proposal was revised to use alternative methodologies that did not involve enhanced potential pandemic pathogen research.

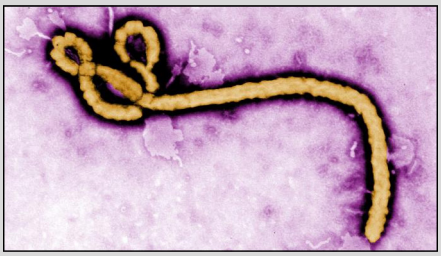
According to CDC officials, enhanced potential pandemic pathogen research is not typically the type of research the agency funds, and the agency had not received any funding requests for such work as of September 2022. According to FDA officials, the agency has also not funded research related to enhanced potential pandemic pathogens.

Beyond the Framework, HHS and its agencies have other programs in place that are not specifically focused on enhanced potential pandemic pathogens, but may provide additional oversight. Specifically,

- **Federal Select Agent Program.** The Federal Select Agent Program regulates the possession, use, and transfer of certain hazardous pathogens and toxins, which are designated as select agents because they have the potential to pose a severe threat to human, animal, or plant health and safety. Under this program, the CDC's Division of Select Agents and Toxins (DSAT), is responsible for developing and maintaining a list of select agents that have the potential to pose a severe threat to public health and safety. Specifically, in developing and maintaining the list, CDC must assess (1) the effect on human health of exposure to the agent or toxin; (2) the degree of contagiousness of the agent or toxin and the methods by which the agent or toxin is transferred to humans; (3) the availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin; and (4) any other criteria, including the needs of children and other

Examples of Select Agents

The Ebola virus is highly lethal and can cause severe illness and death in humans from hemorrhagic fever. Case fatality rates average 50 percent and can reach 90 percent. The Ebola virus caused an epidemic from 2014-2016 that ended with more than 28,600 cases and 11,325 deaths. The Centers for Disease Control and Prevention (CDC) have listed the Ebola virus as a select agent.



The filamentous and curved morphology of an Ebola virus particle.

Source: The Centers for Disease Control and Prevention (CDC) (information, photos), World Health Organization (information). | GAO-23-105455

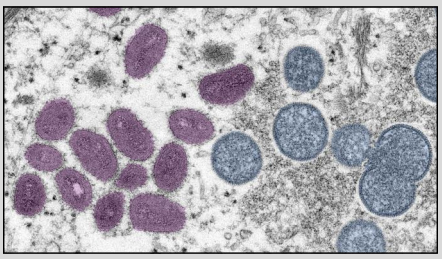
[23]Specifically, all three proposals were referred for departmental review by National Institute of Allergy and Infectious Diseases.

[24]Two of these projects had originally been awarded in 2013 and were subject to the 2014 funding pause. Those projects were subsequently reviewed in 2018 under the Framework policy and were approved to continue.

vulnerable populations.[25] CDC conducts periodic inspections of entities—including research institutions—that possess, use, or transfer these agents.[26] Some pandemic pathogens, such as the influenza strain that caused the 1918 pandemic, are select agents. Generally, laboratories and other entities that possess, use, or transfer these select agents must register with CDC, and must develop explicit biosecurity and biosafety plans and procedures that are reviewed by CDC inspectors.[27]

Examples of Select Agents Continued

The mpox virus is part of the same family of viruses as the virus that causes smallpox. One strain of the virus—the Congo Basin clade—is capable of causing severe illness with a fatality rate of 10 percent. It has been listed by the CDC as a select agent. The strain responsible for the 2022 outbreak is the West African clade, and symptoms are milder and rarely fatal. The West African clade is not listed as a select agent.



Mature (left) and immature (right) mpox virus particles.

Source: The Centers for Disease Control and Prevention (CDC) (information, photos), World Health Organization (information). | GAO-23-105455

- **Dual use research of concern (DURC) policies.** Certain types of research conducted for legitimate purposes can also be utilized for harmful purposes. Such research is called "dual use research." Dual use research of concern (DURC) is the subset of life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that also could be directly misapplied to pose a significant threat to public health, safety, or national security. The federal government's DURC policies aim to strengthen institutional oversight of high-risk life sciences research by providing guidance to its agencies and research institutions on identifying research of concern. DURC policies specify a list of agents—all of which are also on the select agent list— and types of experiments that warrant assessment for the potential to involve DURC. DURC policy requires researchers to identify potential DURC research, and institutions to assess risk posed by such research and develop risk-mitigation plans. Funding agencies are responsible for reviewing and approving the risk mitigations plans. On a biannual basis, agencies report a list of DURC-related research to the Assistant to the President for Homeland Security and Counterterrorism. Research that enhances the transmissibility or virulence of certain potential pandemic pathogens could be subject to DURC.

All three programs—the Framework, Federal Select Agent Program, and DURC—applied to two of the three research proposals noted above that were referred for departmental review under the Framework. Both of the

[25]42 U.S.C. § 262a(a)(1)(B).

[26]The Federal Select Agent Program is jointly managed by CDC and the Department of Agriculture, with the Department of Agriculture responsible for overseeing the use of select agents and toxins that have the potential to pose a severe threat to animal or plant health or animal or plant products. 7 C.F.R Part 331 and 9 C.F.R Part 121 (2022); 42 C.F.R. Part 73 (2021).

[27]See 42 C.F.R. §§ 73.7, 73.12 (2021).

proposed research projects involved highly pathogenic avian influenza, a pathogen with pandemic potential that is also a select agent and included in the DURC policies as well.[28] According to ASPR, CDC, and NIH officials, there is some coordination and information sharing among the programs. For example, CDC officials told us that key officials from the Select Agent Program are members of the departmental review group and that they provide biosafety and biosecurity recommendations in the context of the group's review of a specific proposal.

During the course of our review, in February 2022, NIH tasked NSABB with evaluating and providing recommendations on the scope and effectiveness of OSTP's guidance governing research with enhanced potential pandemic pathogens, the Framework and DURC.[29] HHS and OSTP officials told us that both the Framework and DURC policies are subject to periodic review. According to OSTP officials, this particular review was part of a broader review of biodefense policies in response to the President's January 2021 national security memo, which required a coordinated federal review of health security policies and strategies for reducing the risk of deliberate or accidental biological events.[30] NIH held

[28]GAO previously examined the effectiveness of the Federal Select Agent Program in oversight of select agents and recommended that CDC take steps to improve the elements of effective oversight. See GAO, *High Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, GAO-18-145 (Washington, D.C.: Oct. 19, 2017).CDC agreed with and implemented our recommendations.

[29]In January 2020, HHS charged NSABB with providing recommendations to OSTP and HHS on balancing considerations regarding security and public transparency when sharing information about research involving enhanced potential pandemic pathogens as well as evaluating OSTP's policy guidance on overseeing this research and federal DURC policies. The charge was subsequently revised in 2022 to focus on review and evaluation of OSTP's guidance and HHS's Framework as well as DURC policies.

[30]The White House, *National Security Memorandum on the United States Global Leadership to Strengthen the International COVID-19 Response and to Advance Global Health Security and Biological Preparedness,* (Washington, D.C.: Jan. 21, 2021). Subsequently, in October 2022, the White House released the *National Biodefense Strategy and Implementation Plan for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security,* which updates the 2018 *National Biodefense Strategy,* and pushes for broader concerted effort by federal, state, and local governments to assess, prevent, prepare for, and respond to biological threats. Under this plan, the White House has tasked NSC and OSTP with leading an inter-departmental effort to develop and provide guidance for rigorous life sciences research biosafety and biosecurity norms and oversight and monitoring programs in all sectors worldwide. This includes completing the interagency review of efforts to strengthen responsible conduct for biological research and develop and operationalize interagency plans.

two public listening sessions in April and June 2022 to gather public input on the OSTP's guidance, the Framework and DURC. More recently, NIH convened a virtual meeting of the NSABB on September 21, 2022. The meeting included an update from the NSABB on its work and public comment on its preliminary findings and draft recommendations. According to NIH, NSABB will discuss draft findings and recommendations in the coming months.

HHS Framework for the Oversight of Research Involving Enhanced Potential Pandemic Pathogens Does Not Fully Meet Key Elements of Effective Oversight

The oversight provided by the Framework does not fully meet key elements of effective oversight previously identified by GAO.[31] In particular, the Framework has oversight shortcomings related to two key elements—performing reviews and transparency.

HHS Lacks Assurance That All Relevant Research Proposals Are Referred for Departmental Review

The Framework requires funding agencies to refer proposed research that is "reasonably anticipated to create, transfer or use enhanced potential pandemic pathogens" for departmental review. The departmental review group can only review research that a funding agency has referred for departmental review. Yet, the Framework does not articulate a standard for what "reasonably anticipated" means.

Key element of effective oversight

Ability to perform reviews

The organization conducting oversight should have the ability to perform reviews, including the working knowledge necessary to review compliance with requirements.

Source: GAO. | GAO-23-105455

According to a key element of effective oversight, the organization conducting oversight should have the ability to perform reviews, including the working knowledge necessary to review compliance with requirements. Unclear standards for referral allow for subjective and inconsistent interpretation, and as a result, HHS may not have the opportunity to review all research proposals involving enhanced potential

[31]In 2008, we applied these elements to the area of nuclear safety oversight. In a 2017 report, we expanded the applicability of these five elements to the oversight of high-containment laboratories by the Federal Select Agent Program. See GAO, *Nuclear Safety: Department of Energy Needs to Strengthen Its Independent Oversight of Nuclear Facilities and Operations*, GAO-09-61 (Washington, D.C.: Oct. 23, 2008) and GAO, *High-Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, GAO-18-145 (Washington, D.C.: Oct. 19, 2017).

pandemic pathogens. The Framework refers to the 2016 NSABB report for examples of research that would and would not be considered to involve enhanced potential pandemic pathogens. However, these examples repeat the definition without providing specificity or articulating a standard for "reasonably anticipated."[32]

Experts we spoke with also noted there was a lack of clarity in the Framework's definition of research subject to departmental review. Specifically, the phrase "reasonably anticipated" allows for subjective interpretation and covers a range of certainty regarding the intent of the research and the likelihood of the results. For example, one of the subject matter experts we spoke with told us the phrase could be interpreted to mean that it is more likely than not that research will result in an enhanced potential pandemic pathogen, whereas to others it could mean that the research is certain to result in an enhanced potential pandemic pathogen.

According to HHS and CDC officials, the Framework's definition of research to be referred allows for subjective interpretation of what is reasonably anticipated to result in enhanced potential pandemic pathogens and acknowledged that additional clarity would be helpful. In contrast, NIH officials told us that the criteria for referral in the Framework are well defined and adequate. However, the NIH institute that is most directly involved in research with potential pandemic pathogens—NIAID—developed its own guidance for NIAID staff on how to determine whether a research proposal should be referred for departmental review, suggesting that additional clarity was needed.[33] In this guidance, it advises NIAID staff to err on the side of inclusion when identifying research that may involve enhanced potential pandemic pathogens.

Until HHS works with its funding agencies to develop and document a standard for "reasonably anticipated," the Framework allows for subjective and potentially inconsistent interpretations of the criteria for determining which research proposals fall under the scope of the Framework. Consequently, HHS cannot ensure that funding agencies are

[32]National Science Advisory Board for Biosecurity, *Recommendations for The Evaluation And Oversight Of Proposed Gain-Of-Function Research*, May 2016.

[33]As of September 2022, all research reviewed by the HHS departmental review group were referred by NIAID, one of the 27 components that make up NIH. Within NIH, NIAID is most directly involved in supporting or conducting research with potential pandemic pathogens.

referring all proposed research involving enhanced potential pandemic pathogens for departmental review.

HHS's Departmental Review Process Lacks Transparency

HHS lacks transparency regarding the composition of the departmental review group. This lack of transparency impeded our ability to assess whether those conducting departmental review are equipped with appropriate technical expertise. Furthermore, HHS lacks transparency regarding how the departmental review group applies the Framework's review criteria.

Key elements of effective oversight

Transparency

The organization should provide access to key information, as applicable, to those most affected by operations.

Technical expertise

The organization conducting oversight should have sufficient staff with the expertise to perform sound safety and security assessments.

Source: GAO. | GAO-23-105455

Composition of the departmental review group

HHS lacks transparency regarding the composition of the departmental review group. According to one of the key elements of effective oversight—transparency—the organization conducting oversight should provide access to key information, as applicable, to those most affected by operations. Key information includes information regarding the composition of the departmental review group and selection criteria for the review group membership. However, HHS does not publicly share the qualifications or expertise of those involved in the review process. Because little is known about the composition of the departmental review group, it is not clear whether the departmental review group is equipped with the full range of technical expertise needed to critically evaluate risks associated with proposed research involving enhanced potential pandemic pathogens.

The Framework lists the disciplines that should be represented in the review group, but does not identify the qualifications of the review group members or which HHS agencies are to be represented in the group.[34] Policymakers and the research community, including the experts we spoke with, as well as presenters at NSABB meetings, criticized the lack of transparency about the composition of the departmental review group.

[34]The Framework specifies that the following disciplines should be represented during the department-level review: scientific research, biosafety, biosecurity, medical countermeasure development and availability, law, ethics, public health preparedness and response, biodefense, select agent regulations, and public health policy, as well as the funding agency perspectives and other relevant areas.

This practice is also inconsistent with other HHS research review protocols that identify the selection process for reviewers. For example, NIH publicly shares the selection criteria—including expertise requirements and individual qualifications—for reviewers who participate in the standard grant review process. In addition, NIH publicly shares the rules, responsibilities, and possible consequences for any actions that may threaten the integrity of its peer review process.[35]

According to HHS's standard operating procedures for departmental review, the review group members are selected by the departmental review group Chair and confirmed by the Assistant Secretary for Preparedness and Response. However, the guidance is unclear as to the detailed selection process and criteria for the members and details regarding the appointment and tenure of the Chair.

This lack of transparency regarding the composition of the departmental review group impeded our ability to assess whether the Framework meets another key element of effective oversight—technical expertise. This key element states that the organization conducting oversight should have sufficient staff with the expertise to perform sound safety and security assessments.

The Chair of the departmental review group stated the confidentiality of review group members was intended to protect the privacy concerns and personal vulnerabilities of the members and maintain the integrity of the review process. For example, HHS officials told us that agency staff have faced threats to their personal safety related to their perceived involvement in gain-of-function research. Given the heightened concern about the risks posed by this type of research, and the safety of scientists, officials told us that there is a need to balance protection of personal vulnerabilities and transparency. However, HHS was able to share some non-sensitive information about the composition of the review group and expertise of those involved. For example, the Chair of the

[35]NIH publicly shares its selection process (NIH, "How Scientists Are Selected to Be Members of a Chartered Review Group" (Bethesda Md.: April 07, 2022), accessed Oct. 12, 2022. https://public.csr.nih.gov/ForReviewers/BecomeAReviewer/CharteredReviewers and roles and responsibilities of its peer reviewers (NIH, "Maintaining Security and Confidentiality in NIH Peer Review: Rules, Responsibilities and Possible Consequences" (Bethesda Md.: December 30, 2021), accessed Oct. 12, 2022. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-044.html). For details on how NIH shares non-sensitive key information about its peer reviewers, see NIH peer review policies and practices website (NIH, "Policy & Compliance: Peer Review Policies and Practices" (Bethesda Md.: June 12, 2022), accessed Oct. 21, 2022. https://grants.nih.gov/policy/peer/index.htm.

committee told us that the departmental review group comprises HHS officials with appropriate technical expertise. In particular, as CDC officials confirmed, the Select Agent Program is represented in the departmental review group, fulfilling the requirements outlined in the Framework. By working with funding agencies to identify and share non-sensitive information about the composition of the review group—such as the qualifications or expertise of those who are involved in the review process— researchers, Congress and the public would have greater assurance that individuals with the appropriate expertise are conducting reviews of research involving enhanced potential pandemic pathogens.

Application of the review criteria

HHS also lacks transparency regarding its review process under the Framework. According to the transparency element of effective oversight, the organization conducting oversight should provide access to key information, as applicable, to those most affected by operations. This key information includes how the criteria are applied in the departmental group's review. However, HHS does not publicly share how the review group assesses the research proposals and applies the review criteria.

Although the Framework lists the evaluation criteria that the departmental review group must consider, HHS is not transparent about how those criteria are applied when evaluating research proposals and how they result in recommendations to the funding agency. Multiple experts we spoke with stated that transparency within HHS's departmental review process is important to understanding the application of the departmental evaluation criteria. During an NSABB listening session in April 2022, other members of the research community raised similar concerns. For example, one biosafety specialist noted that given the broad range of biosafety and biosecurity practices among researchers and institutions, without greater transparency in how the departmental review group applies criteria, it is unclear how the departmental review group can assess an institution's capacity to conduct research safely and securely. This specialist further noted that the public's awareness of research assessments of what levels of risk are acceptable, as well as public engagement in the process of establishing a minimum standard for biosafety practices and policies, are essential to the standard's dissemination.

HHS officials told us that departmental review is a pre-funding review, and as such, they do not want to compromise intellectual property by

sharing details about the research assessment process.[36] Similarly, according to NIH, information about HHS's pre-funding reviews of specific proposals are not shared publicly in order to preserve confidentiality and to allow for candid critique and discussion of individual proposals.

We acknowledge the sensitivity and intricacy of departmental review. Those most involved in the review process—HHS and funding agencies—are best positioned to identify non-sensitive information that could be shared with the public. For example, NIH was able to provide a public description of its own review and referral process in its response to congressional inquiries.[37] Furthermore, HHS officials told us the departmental review group critically evaluates the proposal against each criterion. They told us that to assess, for example, an institution's capacity to conduct work safely, the departmental review group examines past history of adherence to biosafety and biosecurity practices, policies, and procedures. HHS has an opportunity to balance the need to preserve the integrity of the review process while improving transparency by sharing this type of information with researchers, Congress, and the public about how criteria are applied.

By working with its funding agencies to identify and share non-sensitive information about how HHS, in coordination with its funding agencies, conducts reviews and makes funding recommendations, researchers, Congress, and the public would have greater assurance that departmental review provides meaningful and effective suggestions to address biosafety and biosecurity concerns about research involving enhanced potential pandemic pathogens.[38] Moreover, doing so could enhance public confidence in the department's oversight as well as ensure the agency's goal to exemplify and promote the highest level of

[36]Descriptions of research proposals reviewed by the departmental review group are made public upon funding agency's decision to fund the research (https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx).

[37]Letter from NIH Director Francis Collins to Senator Charles Grassley, July 28, 2021, https://www.grassley.senate.gov/download/national-institutes-of-health-to-grassley_-covid-origins-grant-oversight

[38]For example, NIH's peer review policies and practices website (https://grants.nih.gov/policy/peer/index.htm) provides detailed guidelines regarding the peer review process, including review criteria, scoring guidance for reviews, rules about conflict of interest, and additional review considerations. For example, the NIH grant application scoring system is used to encourage reliable scoring of applications. The website contains information about detailed scoring procedures and examples in assigning impact scores and individual criterion scores in NIH peer review.

scientific integrity, public accountability, and social responsibility in the conduct of science.

Independent Reviews of Intramural and Extramural Research for Referral

Key element of effective oversight

Independence

The organization conducting oversight should be structurally distinct and separate from the entities it oversees.

Source: GAO. | GAO-23-105455

Under the Framework, proposed intramural and extramural life sciences research that is being considered for funding and that has been determined by the funding agency as reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens is subject to additional departmental review. The Framework applies to funding for proposed research and operates before funding of the research. Therefore, HHS's oversight of such research begins with, and relies on, funding agencies to identify, flag, and refer them for additional review.

According to a key element of effective oversight, to be independent, the organization conducting oversight should be structurally distinct and separate from the entities it oversees. Furthermore, OSTP guidance for reviewing enhanced potential pandemic pathogen research suggests departments and agencies are to vest oversight for their review mechanisms in offices that do not report to the head of the agency component that is proposing to fund such research. According to agency officials, funding agencies incorporate the reviews for referrals with their DURC reviews, which are performed by independent internal committees. Enhanced potential pandemic pathogen research is not typically the type of research that CDC or FDA funds. However, officials from CDC and FDA told us that both agencies would review research involving enhanced potential pandemic pathogens through their DURC review processes.[39] According to NIH documents and officials, NIH incorporates its review for referrals with its DURC review process. For example, as the institute conducting and funding the most research on enhanced potential pandemic pathogens, NIH developed procedures to help with an independent review process for both its extramural and intramural research proposals. [40] Specifically,

[39]CDC officials said that enhanced potential pandemic pathogen research is not typically the type of research the agency funds, but they would review such research proposals as they would for any proposals they receive involving dual use research of concern. Agency officials said there is no separate review mechanism for enhanced potential pandemic pathogen research proposals. FDA provided a directive outlining its internal process for reviewing enhanced potential pandemic pathogen research proposals with its DURC review panel, including a review by the Director of the Office of Laboratory Safety.

[40]As of September 2022, all research reviewed by the departmental review group under the Framework were referrals from NIAID, an institute of NIH.

- Extramural research review: NIAID established a pre-departmental review committee and developed standard operating procedures outlining the institute's review process under the Framework. According to NIAID's standard operating procedures, at the institute-level, NIAID employs a two-stage review process to determine referrals: 1) program officer review to identify research that may be subject to the Framework, and 2) institute-level committee review of the research to determine referrals for departmental review.
- Intramural research review: NIAID leverages the NIH's existing internal independent review process to review its intramural research for referral. Specifically, NIH's DURC institutional review entity, comprising officials from NIH offices and component institutes, review intramural research protocols that may involve DURC. During the course of our review, NIH updated its DURC review policy for intramural research in September 2022 to require NIH's DURC institutional review entity to assess proposed intramural research for enhanced potential pandemic pathogens. According to NIH officials, the institutional review entity would determine whether to refer intramural research for departmental review based on the assessment.

HHS Enforcement Authority

Key element of effective oversight

Enforcement authority

The organization should have clear and sufficient authority to require that entities achieve compliance with requirements.

Source: GAO. | GAO-22-105455

Under the Framework, a departmental review is layered onto funding agencies' standard grants process. According to a key element of effective oversight, the organization conducting oversight should have clear and sufficient authority to require entities to achieve compliance with requirements. Under the Framework, HHS reviews research that has been referred for departmental review and makes recommendations to the funding agencies, which have the authority to determine whether to fund research or incorporate the recommended measures into the grant terms and conditions and oversee grantee compliance.[41] Our analysis of the two research projects that NIAID funded following departmental review showed that the terms and conditions added to the awards were consistent with the departmental review group's recommendations. For example, NIAID added additional reporting requirements to the awards based on the departmental review group's recommendations.

[41]HHS officials told us that during the development of the 2017 OSTP Guidance, the National Security Council determined that only the funding agency has the authority to determine whether to award funds and to impose conditions on the award of such funds.

HHS Faces Challenges Overseeing Research with Newly Emerged Potential Pandemic Pathogens during a Public Health Emergency

Under the DSAT program, CDC must maintain a list of pathogens that pose a severe threat to public health.[42] CDC faces tradeoffs, however, between extending DSAT oversight to a newly emerged pandemic pathogen—for example, SARS-CoV-2, the virus responsible for the COVID-19 pandemic—and public health response activities (see text box). While adding a pathogen to the select agent list would allow CDC to oversee potentially high-risk research with the newly added select agent, this oversight could also impede the public health response activities during a pandemic by, for example, subjecting diagnostic and medical countermeasure development activities to DSAT's reporting and inspection requirements.

Centers for Disease Control and Prevention (CDC) Oversight of Research with SARS-CoV-2

In November 2021, CDC added specific Severe Acute Respiratory Syndrome (SARS) coronaviruses—SARS-CoV/SARS-CoV-2 chimeras—to the select agent list. These chimeras, which could have resulted in a new potential pandemic virus, are laboratory-created viruses that contain genetic material derived from two distinct viruses. The regulated chimeric viruses are explicitly limited to those that result from deliberately manipulating SARS-CoV-2 to incorporate genetic material from SARS-CoV, which is currently a select agent.

These chimeras were added to the select agent list after an institution's official voluntarily informed DSAT in April 2021 of planned research that could enhance a pandemic pathogen, SARS-CoV-2, according to CDC officials. In its interim final rule to add these chimeras to the select agent list, CDC noted that these experiments carried a significant potential risk of creating a chimeric virus that, if released, would result in a public health emergency requiring complicated and expensive response efforts, such as those seen during the COVID-19 pandemic.

CDC officials told us that they were able to add these specific SARS chimeric viruses to the select agent list because regulating these viruses would not interfere with the public health response. However, the addition of these SARS chimeras to the select agent list does not prevent research to make other SARS chimeras. For example, the results of research conducted at Boston University posted in October 2022 to create a chimera from two different SARS-CoV-2 strains is not covered by the Federal Select Agent Program because the research did not use genetic material from SARS-CoV and SARS-CoV-2.

Source: GAO analysis. | GAO-23-105455

[42]The HHS Secretary is required to establish and maintain a list of each biological agent and toxin that has the potential to pose a severe threat to public health and safety. 42 U.S.C. § 262a(a)(1)(A).

Federal law authorizes CDC to exempt individuals or entities from DSAT requirements if it is determined an exemption is necessary to provide for the timely participation of the person or entity in the response to a public health emergency involving the listed agent.[43] This exemption authority gives CDC flexibility to determine which requirements to apply to specific individuals or entities. Such authority could allow for response activities such as diagnostic testing and medical countermeasure development that might otherwise be limited by the application of the full range of the DSAT requirements, while still allowing oversight of other research with the select agent. However, CDC can only exempt individuals or entities from DSAT's regulatory requirements for a maximum of 60 days, which may not be sufficient during an ongoing pandemic, such as the COVID-19 pandemic that had been ongoing for more than 2 years at the time of this report.[44]

CDC officials agree this is a limitation. They told us they have not added SARS-CoV-2 to the select agent list because doing so would impede the pandemic public health response. For example, if CDC were to add SARS-CoV-2 to the select agent list during the COVID-19 pandemic, response efforts, such as important diagnostic work to track the spread of SARS-CoV-2, could be impeded due to the Federal Select Agent Program requirement to report each time a select agent is identified in patient samples. Additionally, research and medical countermeasure development efforts (such as COVID-19 therapeutics to prevent severe disease or death) could be slowed. This is because of the Federal Select Agent Program requirement that manipulation of the pathogen necessary to do this work only occur in laboratories that are registered with the Federal Select Agent Program and be performed by researchers who have undergone a background check.

CDC officials told us they have had discussions with HHS leadership concerning needs and challenges regarding the DSAT program, including the need for proposed legislative solutions. However, HHS leadership did not provide further details, leaving it unclear if HHS is considering possible changes to the DSAT program that would provide CDC with the

[43]42 U.S.C. § 262a(g)(3); 42 C.F.R. § 73.5(e) (2021).

[44]The Secretary of HHS is authorized to exempt individuals or entities from DSAT regulations during a public health emergency, but these exemptions are limited to a 30-day period with a maximum extension of an additional 30 days.

flexibility to address the potential risks this program poses with respect to the limitation with the exemption period during a public health emergency.

Federal agencies are required to integrate risk management activities into their program management to help ensure they are effectively managing risks that could affect the achievement of agency objectives, according to the Office of Management and Budget's Circular A-123. In addition, federal internal control standards state that management should identify, analyze, and respond to risks related to achieving defined objectives. Without assessing and documenting the risk posed by the limitations in the duration of its existing exemption authority for public health emergencies, and taking any needed actions to mitigate any identified risks—including seeking legislative authority as needed—CDC will continue to face tradeoffs between impeding public health response efforts and allowing high-risk research involving known pandemic pathogens to be conducted without appropriate CDC oversight.

HHS Oversight of Privately Funded Enhanced Potential Pandemic Pathogen Research Is Limited

HHS's ability to oversee and regulate privately funded enhanced potential pandemic pathogen research is limited. Specifically, HHS does not conduct oversight of privately funded research, including enhancement of potential pandemic pathogens, if those pathogens are not select agents. For its part, the Framework applies only to grant applications submitted to HHS funding agencies. OSTP officials told us that the OSTP guidance and corresponding Framework were aimed at federally funded research because, at the time the guidance was developed, the understanding was that federal funding supported the majority of enhanced potential pandemic research.

The DURC policies apply only to institutions that receive federal funding for life science research and conduct research with any of the 15 agents or toxins listed in the policy, regardless of the funding source for that research. OSTP and White House National Security Council officials were unable to provide information on the extent to which enhanced potential pandemic pathogen research is privately funded. OSTP officials told us that the scope of federal policies is under consideration as part of NSABB's current ongoing review of both the Framework and the DURC policies.

Of HHS's existing oversight, only the DSAT program oversees research conducted at privately funded institutions. However, its oversight is limited to its list of select agents and toxins. HHS does not have the responsibility or authority, under the Framework, the DURC policies, or the DSAT program, to license or regulate new laboratories unless use or storage of

select agents or toxins is planned; as a result, it may not have knowledge of privately funded laboratories that are not registered with the Federal Select Agent Program.[45]

HHS and its agencies' missions include identifying and preparing for public health threats. Federal internal controls standards require that federal agencies use, identify, and obtain quality information necessary to achieve their objectives, including identifying and addressing public health risks that could result from research with potential pandemic pathogens. A lack of knowledge about the scope and location of privately funded research being conducted means that there is a risk that an adverse public health event could result from unknown actors in unknown locations conducting high-risk research.

In 2009, we recommended that the National Security Advisor, in consultation with the Secretary of Health and Human Services, among others, identify a single entity charged with periodic government-wide strategic evaluation of high-containment laboratories.[46] The White House disagreed with the recommendation and the recommendation was not implemented. White House National Security Council staff we spoke with in September 2022 stated they have no position to share on this recommendation. We maintain that implementing this recommendation would provide the U.S. government with information that could be used to assess the risk posed by gaps in oversight of privately funded research with recently emerged potential pandemic pathogens and allow HHS to determine whether additional authorities are needed to address these risks.

Conclusions

Research involving potential pandemic pathogens is crucial for ensuring the nation's ability to prepare for, respond to, and recover from public health threats, such as COVID-19 and mpox. However, it also comes with risks. HHS has taken steps with the development of the Framework to strengthen oversight of research with potential pandemic pathogens.

[45]Institutions that are registered with the Federal Select Agent Program must provide information on the specific laboratories where select agents and toxins will be used or stored, the specific select agents or toxins in each laboratory, and a description of the work for each select agent or toxin.

[46]See GAO, *High-Containment Laboratories: National Strategy for Oversight is Needed.* GAO-09-574 (Washington, D.C.: Sept. 21, 2009). In this report, we noted the increase in the number of high-containment laboratories had occurred across federal, state, academic, and private sectors. The Executive Office of the President (EOP) provided no comments to the report in 2009. In 2012, the EOP responded to GAO to note disagreement with the recommendation.

However, until HHS works with its funding agencies to develop and document a standard for "reasonably anticipated," the Framework allows for subjective and potentially inconsistent interpretations of the criteria for referral, potentially leaving HHS without the assurance that funding agencies are referring all the research proposals that should be referred for departmental review. Furthermore, by working with its funding agencies to identify and publicly share non-sensitive information about the departmental review process—including information on the composition and expertise of those involved in the review process, as well as how the evaluation criteria are applied—HHS would provide researchers, Congress and the public with greater assurance that the departmental review provides meaningful and effective suggestions to address biosafety and biosecurity concerns about research involving enhanced potential pandemic pathogens.

Moreover, HHS faces oversight gaps beyond the Framework. Specifically, until HHS and CDC assess and document the risks posed by the limitations of the existing DSAT exemptions for public health emergencies—including seeking any necessary legislative authority—as it deliberates changes to the DSAT program, CDC will continue to face tradeoffs between impeding public health response efforts and allowing high-risk research involving known pandemic pathogens to be conducted without appropriate CDC oversight.

We maintain that implementing our 2009 recommendation to charge a single federal entity with periodic government-wide strategic evaluations of high-containment laboratories would help HHS assess the risks posed by the lack of oversight of privately funded research that enhances potential pandemic pathogens, and develop mitigation plans, as needed.

Recommendations

We are making a total of three recommendations to HHS:

The Secretary of Health and Human Services should work with HHS funding agencies to develop and document a standard for "reasonably anticipated" to ensure consistency in identifying research for departmental review that is "reasonably anticipated to create, transfer or use enhanced potential pandemic pathogens." (Recommendation 1)

The Secretary of Health and Human Services should work with HHS funding agencies to identify and share non-sensitive information with researchers, Congress, and the public about the departmental review process for research involving enhanced potential pandemic pathogens, including information on composition and expertise of those involved in

the review process and how the evaluation criteria are applied. (Recommendation 2)

As HHS and CDC deliberate any changes to the DSAT program, the Director of the Centers for Disease Control and Prevention should assess and document the risk posed by the limitations of the existing DSAT exemptions for public health emergencies and seek legislative authority as needed. (Recommendation 3)

Agency Comments and Our Evaluation

We provided a draft of this report for advance review and comment to OSTP, the National Security Council, and HHS. National Security Council officials provided a technical comment, and OSTP officials told us they had no comments. HHS provided written comments, which we have reprinted in appendix I. HHS neither agreed nor disagreed with our first two recommendations to develop and document a standard for "reasonably anticipated" and share non-sensitive information about the departmental review. HHS stated that the department is committed to ensuring careful review and consideration of guidance to enhance the existing Framework and increase transparency. HHS further cited the ongoing work of the NSABB in evaluating the Framework, among other oversight policies and programs, and developing recommendations. HHS noted that the department expects this work to inform its future actions. HHS concurred with our third recommendation that HHS and CDC should assess and document risks posed by the limitations of the existing DSAT exemptions and seek legislative authority as needed. HHS also stated that CDC is collaborating with HHS and the National Security Council to outline existing gaps and potential improvements to the Federal Select Agent Program.

We are sending copies of this report to the Secretary of Health and Human Services and appropriate congressional committees. The report is also available at no charge on the GAO website at https://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or at DeniganMacauleyM@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix III.

Mary Denigan-Macauley
Director, Health Care

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Appendix I: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

December 19, 2022

Mary Denigan-Macauley
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Denigan-Macauley:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, **"PUBLIC HEALTH PREPAREDNESS: HHS Could Improve Oversight of Research Involving Enhanced Potential Pandemic Pathogens" (GAO-23-105455SU).**

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT - "PUBLIC HEALTH PREPAREDNESS: HHS COULD IMPROVE OVERSIGHT OF RESEARCH INVOLVING ENHANCED POTENTIAL PANDEMIC PATHOGENS" (GAO-23-105455SU)

Recommendation 1

The Secretary of Health and Human Services should work with HHS funding agencies to develop and document a standard for "reasonably anticipated" to ensure consistency in identifying research for departmental review that is "reasonably anticipated to create, transfer or use enhanced potential pandemic pathogens."

HHS Response

HHS is committed to ensuring that it carefully reviews, considers, and incorporates guidance to enhance its existing framework. Earlier this year, the Acting NIH Director delivered a charge to the National Science Advisory Board for Biosecurity (NSABB) to review the scope and effectiveness of the USG's biosecurity policy frameworks governing research with enhanced potential pandemic pathogen (ePPP) and dual use research of concern (DURC). Specifically, the charge directed review of the White House Office of Science and Technology Policy's *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight* (OSTP P3CO Policy Guidance) and HHS's implementation of the OSTP guidance—the HHS P3CO Framework, as well as USG policies for the oversight of DURC.

The NSABB's final recommendations are anticipated in the coming months and will inform interagency and HHS deliberations about both the OSTP P3CO Policy Guidance and the HHS P3CO Framework to ensure we have robust policies and guidance in place. HHS will provide a future update to GAO in its Statement of Actions letter which is required by OMB Circular A-50 and 31 U.S.C. 720.

Recommendation 2

The Secretary of Health and Human Services should work with HHS funding agencies to identify and share non-sensitive information with researchers. Congress, and the public about the departmental review process for research involving enhanced potential pandemic pathogens, including information on composition and expertise, of those involved in the review process and how the evaluation criteria are applied.

HHS Response

HHS is committed to ensuring that it carefully reviews, considers, and incorporates guidance to increase transparency in the oversight of funding for research involving enhanced potential pandemic pathogens. In January 2020, the NIH Associate Director for Science Policy delivered a charge to the National Science Advisory Board for Biosecurity (NSABB) to provide recommendations regarding the balance between security and public transparency when sharing information about enhanced PPP research. The Working Group that is reviewing and evaluating the P3CO policy provided an update on its efforts during the NSABB September 22, 2022, meeting, including their efforts to enhance the transparency of the review process.

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT - "PUBLIC HEALTH PREPAREDNESS: HHS COULD IMPROVE OVERSIGHT OF RESEARCH INVOLVING ENHANCED POTENTIAL PANDEMIC PATHOGENS" (GAO-23-105455SU)

The NSABB's final recommendations are anticipated in the coming months and will inform interagency and HHS deliberations about both the OSTP P3CO Policy Guidance and the HHS P3CO Framework to ensure we have robust policies and guidance in place. HHS will provide a future update to GAO in its Statement of Actions letter which is required by OMB Circular A-50 and 31 U.S.C. 720.

Recommendation 3

As HHS and CDC deliberate any changes to the DSAT program, the Director of the Centers for Disease Control and Prevention should assess and document the risk posed by the limitations of the existing DSAT exemptions for public health emergencies and seek legislative authority as needed.

HHS Response

HHS concurs with the recommendation. CDC, including DSAT, is continuing internal efforts and collaborating with HHS and the National Security Council to outline existing gaps and potential enhancements to the Federal Select Agent Program.

Appendix II: National Institutes of Health Oversight of Surveillance of Naturally Occurring Pathogens

This appendix includes information on National Institutes of Health (NIH) oversight of a grant that involved surveillance of naturally occurring pathogens as an example of how oversight is conducted for a grant that does not fall within the Department of Health and Human Services oversight framework for enhanced potential pandemic pathogen research (the Framework).

According to NIH officials, a grant proposal examining the risk of bat Severe Acute Respiratory Syndrome (SARS)-like coronavirus emergence fell outside of the scope of the Framework because novel bat coronaviruses—novel coronaviruses that were found to have been naturally occurring and circulating among bats—had not been shown to infect humans; therefore the viruses being studied did not meet the definition of a potential pandemic pathogen.[1] Additionally, NIH officials told us that the experiments described by the researchers—the EcoHealth Alliance—were not anticipated to increase the virulence or transmissibility of these viruses in humans. NIH funded the research and oversaw it using its standard grant oversight process.

According to the agency's 2021 NIH Grants Policy Statement (Policy Statement), NIH references biosafety standards but does not monitor compliance with those standards. Specifically, NIH requires grantees to comply with Occupational Safety and Health Administration regulations for blood borne pathogens and occupational exposure to hazardous chemicals in labs and Nuclear Regulatory Commission standards and regulations, and recommends that grantees follow the Biosafety in Microbiological and Biomedical Laboratories' guidelines. As appropriate, NIH may reference other policies and programs (e.g., the Federal Select Agent Program), but does not require grantees to submit documented assurance of their compliance with these regulations and guidelines.[2] For example, NIH requires grantees to comply with the Division of Select Agents and Toxins' regulations, but officials told us that the agency relies

[1]National Institutes of Health, Response to Congressional Inquiry, October 20, 2021, https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research. This inquiry stemmed from concerns about the source of the COVID-19 pandemic and U.S. funding of research conducted in a foreign country.

[2]The Policy Statement states that, if requested by the awarding institute or center, recipients should be able to provide evidence of consideration and practice of applicable safety standards.

on the Centers for Disease Control and Prevention to monitor compliance.

NIH requires grantees to provide periodic progress reports describing findings, and NIH may change terms and conditions for subsequent grant awards.[3] For example, NIH monitored EcoHealth Alliance's progress reports and added a reporting measure when agency staff identified a risk. Specifically, after EcoHealth Alliance's year 2 progress reported the successful construction of SARS-like chimeras, NIH flagged it as a risk, and added a special condition to the 3rd year Notice of Award. This condition referenced a letter requiring work stoppage with MERS-like or SARS-like chimeras if the manipulated viruses showed a certain amount of increased growth when comparing the manipulated strains to the parental backbone strain. Officials told us that this work involved new viruses and there was a lack of data on virulence and transmissibility, therefore increased growth was selected to serve as an indicator that additional review of the research would be needed. According to NIH officials, they found that EcoHealth Alliance did not adequately monitor the activities of its subawardees and took action to terminate this part of the grant award According to NIH, the agency will work with EcoHealth Alliance to renegotiate the aims and objectives of the grant before taking additional action.[4]

[3]The Policy Statement requires that grantees report at least annually on budget information, but NIH has the flexibility to specify the elements for reporting and require more frequent reporting. The grant terms and conditions include requirements for the content and frequency of the progress reports. Progress reports include sections to report whether the major goals of the research have changed, accomplishments during the previous funding period toward those goals, and plans for the next reporting period to accomplish the research goals.

[4]National Institutes of Health, Response to Congressional Inquiry, August, 19, 2022, https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

Mary Denigan-Macauley, (202) 512-7114 or DeniganMacauleyM@gao.gov

Staff Acknowledgments

In addition to the contact named above, Kelly DeMots (Assistant Director), Jasleen Modi (Analyst-in-Charge), Stella Chiang, Kevin Dong, Suhna Lee, Jenna Moody, and Janet Wilson made key contributions to this report. Also contributing were Samuel Amrhein and Jennifer Whitworth.

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Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

THE NATIONAL INSTITUTES OF HEALTH AND ECOHEALTH ALLIANCE DID NOT EFFECTIVELY MONITOR AWARDS AND SUBAWARDS, RESULTING IN MISSED OPPORTUNITIES TO OVERSEE RESEARCH AND OTHER DEFICIENCIES

Inquiries about this report may be addressed to the Office of Public Affairs at Public.Affairs@oig.hhs.gov.

Christi A. Grimm
Inspector General

January 2023
A-05-21-00025

Office of Inspector General

https://oig.hhs.gov

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OFFICE OF AUDIT SERVICES FINDINGS AND OPINIONS

The designation of financial or management practices as questionable, a recommendation for the disallowance of costs incurred or claimed, and any other conclusions and recommendations in this report represent the findings and opinions of OAS. Authorized officials of the HHS operating divisions will make final determination on these matters.

Report in Brief
Date: January 2023
Report No. A-05-21-00025

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF INSPECTOR GENERAL

The National Institutes of Health and EcoHealth Alliance Did Not Effectively Monitor Awards and Subawards, Resulting in Missed Opportunities to Oversee Research and Other Deficiencies

Why OIG Did This Audit

OIG initiated this audit because of concerns regarding the National Institutes of Health's (NIH's) grant awards to EcoHealth Alliance (EcoHealth), NIH's monitoring of EcoHealth, and EcoHealth's use of grant funds, including its monitoring of subawards to a foreign entity.

Our objectives were to determine whether NIH monitored grants to EcoHealth in accordance with Federal requirements, and whether EcoHealth used and managed its NIH grant funds in accordance with Federal requirements.

How OIG Did This Audit

We obtained a list of all NIH awards to EcoHealth and all subawards made by EcoHealth during Federal fiscal years 2014 through 2021 (audit period). Our audit covered three NIH awards to EcoHealth totaling approximately $8.0 million, which included $1.8 million of EcoHealth's subawards to eight subrecipients, including the Wuhan Institute of Virology (WIV).

Our audit methodology was designed to address NIH and EcoHealth's policies, procedures, and internal controls in place to monitor, manage, and use grant funds. We selected and reviewed 150 EcoHealth transactions totaling $2,578,567 across the 3 NIH awards comprised of different types of cost categories for allowability.

What OIG Found

Despite identifying potential risks associated with research being performed under the EcoHealth awards, we found that NIH did not effectively monitor or take timely action to address EcoHealth's compliance with some requirements. Although NIH and EcoHealth had established monitoring procedures, we found deficiencies in complying with those procedures limited NIH and EcoHealth's ability to effectively monitor Federal grant awards and subawards to understand the nature of the research conducted, identify potential problem areas, and take corrective action. Using its discretion, NIH did not refer the research to HHS for an outside review for enhanced potential pandemic pathogens (ePPPs) because it determined the research did not involve and was not reasonably anticipated to create, use, or transfer an ePPP. However, NIH added a special term and condition in EcoHealth's awards and provided limited guidance on how EcoHealth should comply with that requirement. We found that NIH was only able to conclude that research resulted in virus growth that met specified benchmarks based on a late progress report from EcoHealth that NIH failed to follow up on until nearly 2 years after its due date. Based on these findings, we conclude that NIH missed opportunities to more effectively monitor research. With improved oversight, NIH may have been able to take more timely corrective actions to mitigate the inherent risks associated with this type of research.

We identified several other deficiencies in the oversight of the awards. Some of these deficiencies include: NIH's improper termination of a grant; EcoHealth's inability to obtain scientific documentation from WIV; and EcoHealth's improper use of grant funds, resulting in $89,171 in unallowable costs.

OIG oversight work has continually demonstrated that grant-awarding agencies' oversight of subrecipients, whether domestic or foreign, is challenging. The shortcomings we identified related to NIH's oversight of EcoHealth demonstrate continued problems. Compounding these longstanding challenges are risks that may limit effective oversight of foreign subrecipients, which often depends on cooperation between the recipient and subrecipient, and the countries in which the research is performed. Although WIV cooperated with EcoHealth's monitoring for several years, WIV's lack of cooperation following the COVID-19 outbreak limited EcoHealth's ability to monitor its subrecipient. NIH should assess how it can best mitigate these issues and ensure that it can oversee the use of NIH funds by foreign recipients and subrecipients.

What OIG Recommends, and National Institutes of Health's and EcoHealth's Comments

We recommend that NIH ensure that EcoHealth accurately and in a timely manner report award and subaward information; ensure that administrative actions are appropriately performed; implement enhanced monitoring, documentation, and reporting requirements for recipients with foreign subrecipients; assess whether NIAID staff are following policy to err on the side of inclusion when determining whether to refer research that may involve ePPP for further review; consider whether it is appropriate to refer WIV to HHS for debarment; ensure any future NIH grant awards to EcoHealth address the deficiencies noted in the report; and resolve costs identified as unallowable as well as possibly unreimbursed costs.

In written comments, NIH stated that it concurred or generally concurred with our recommendations and provided actions taken or planned to address them, which are more fully described in the report.

We recommend EcoHealth submit progress reports by the required due dates, comply with immediate notification requirements, ensure access to all subrecipient records, properly account for subawards, and refund to the Federal Government $89,171 in unallowable costs.

In written comments, EcoHealth concurred with our recommendation to prepare accurate subaward and consultant agreements but did not directly state whether it concurred with the other recommendations. EcoHealth identified two substantive areas of disagreement with the reported findings: (1) the timeliness of EcoHealth's Year 5 progress report and (2) whether an experiment exhibited enhanced virus growth. Regarding the nine monetary recommendations, EcoHealth stated that it reimbursed NIH for the total reported unallowable costs and provided NIH with details on the amounts of allowable but unreimbursed costs. However, EcoHealth disagreed with OIG's interpretation of Federal requirements for some items of cost.

With respect to EcoHealth's comments regarding the timeliness of EcoHealth's Year 5 progress report, we have no evidence that the progress report, which was initiated on NIH's online portal in July 2019, was fully uploaded to the online portal at that time. Regarding the finding that an experiment exhibited "enhanced growth," our audit did not assess scientific results for any of the experiments or make any determination regarding the accuracy of NIH's or EcoHealth's interpretations of the Years 4 and 5 research results. Our audit found that NIH's own evaluation of the Year 5 progress report concluded that the research was of a type that should have been reported immediately to NIH.

After reviewing NIH's and EcoHealth's comments, we maintain that all of our recommendations are valid.

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INTRODUCTION

WHY WE DID THIS AUDIT

This audit was initiated after the Office of Inspector General (OIG) became aware of concerns regarding the National Institutes of Health's (NIH's) grant awards to EcoHealth Alliance (EcoHealth), NIH's monitoring of EcoHealth, and EcoHealth's use of grant funds, including its monitoring of subawards to a foreign entity.

OIG's oversight has examined NIH's efforts to ensure the integrity and the effective management of its grant application and selection processes, and has reviewed NIH-funded research institutions' compliance with Federal requirements and NIH policies that establish controls for NIH grants, contracts, and other transactions.[1] Prior OIG work highlighted an increased need for transparency in research funding and identified several areas in which NIH could improve how it oversees the more than $30 billion in grants for research it awards each year. More specifically, OIG previously identified NIH's oversight of grants to foreign applicants as a risk to the Department of Health and Human Services (HHS or the Department) in terms of meeting program goals and the appropriate use of Federal funds.[2]

Our oversight work has also consistently found deficiencies with grant-awarding agencies' oversight of subrecipients. NIH must effectively monitor and administer Federal awards to ensure that Federal funding is spent, and associated programs are implemented, in full accordance with statutory and public policy requirements.

OBJECTIVES

Our objectives were to determine whether: (1) NIH monitored grants to EcoHealth in accordance with Federal requirements and (2) EcoHealth used and managed its NIH grant funds in accordance with Federal requirements.

BACKGROUND

National Institutes of Health

NIH is the agency responsible for the Nation's medical and behavioral research. Its mission is to seek fundamental knowledge about the nature and behavior of living systems and to apply that

[1] The Department of Defense and Labor, Health and Human Services, and Education Appropriations Act, 2019, and Continuing Appropriations Act, 2019, P.L. No. 115-245, directed OIG to examine the efforts of NIH to ensure the integrity of its grant application evaluation and recipient selection processes.

[2] *The National Human Genome Research Institute Should Strengthen Procedures in Its Pre-Award Process To Assess Risk for Certain Foreign and Higher Risk Applicants*, A-05-20-00026, August 2021, available at https://oig.hhs.gov/oas/reports/region5/52000026.asp.

knowledge to enhance health, lengthen life, and reduce illness and disability. In Federal fiscal year (FY) 2020, NIH awarded more than $30.8 billion in extramural research awards. In FY 2021, NIH awarded more than $32.3 billion.

NIH comprises 27 Institutes and Centers, each with a specific research agenda often focusing on particular diseases or body systems. The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. NIAID has a unique mandate that requires the Institute to respond to emerging public health threats. Toward this end, NIAID manages a complex and diverse research portfolio that aims to expand the breadth and depth of knowledge in all areas of infectious, immunologic, and allergic diseases, and develop flexible domestic and international research capacities to respond appropriately to emerging and re-emerging disease threats at home and abroad. In FY 2021, NIAID awarded approximately $3.9 billion in research grants.

EcoHealth Alliance

EcoHealth is a global environmental health nonprofit organization dedicated to protecting wildlife and public health from the emergence of disease.[3] According to EcoHealth, its mission is to integrate innovative science-based solutions and partnerships that increase capacity to protect global health by "preventing the outbreak of emerging diseases and safeguarding ecosystems by promoting conservation." EcoHealth is based in New York City and employs administrative and scientific staff including wildlife veterinarians, epidemiologists, biologists, technologists, analytic modelers, and public health professionals. EcoHealth works with local governments, in-country scientists, and policymakers around the world to make changes for the prediction and prevention of infectious disease. EcoHealth is funded primarily by government contracts, grants, and private contributions.

Wuhan Institute of Virology

In one of its grant applications to NIH, EcoHealth described the Wuhan Institute of Virology (WIV) as China's premier institute for virological research. WIV consists of three research departments and one center: the Department of Molecular Virology; the Department of Bio-Control; the Department of Analytical Biochemistry and Biotechnology; and the Virus Resource and Bioinformation Center of China. The application describes WIV as an accredited biosafety level 3 (BSL-3) laboratory.[4] EcoHealth's grant application reported that the laboratory has both an Institutional Biosafety Committee and an Institutional Animal Care and Use Committee.

[3] Accessed at https://www.ecohealthalliance.org/about on August 18, 2021.

[4] Biosafety levels are used to identify the protective measures needed in a laboratory setting to protect workers, the environment, and the public. The four biosafety levels are BSL-1, BSL-2, BSL-3, and BSL-4, with BSL-4 being the highest (maximum) level of containment.

Grant-Related Requirements

Monitoring requirements are addressed through Federal regulations, and departmental and awarding agency policies. The regulations at 45 Code of Federal Regulations (CFR) part 75 establish uniform administrative requirements, cost principles, and audit requirements for HHS awards to non-Federal entities. The regulations describe subrecipient monitoring and management requirements applicable to all non-Federal entities that provide a subaward to carry out part of a Federal program.[5] The HHS awarding agency may impose specific award conditions as needed in accord with 45 CFR § 75.207. The use of grant funds are controlled by the terms and conditions of the award, and EcoHealth's awards incorporate all requirements in part 75.

The HHS Grants Policy Administration Manual (GPAM) establishes HHS policies for the administration of grants and cooperative agreements, including the monitoring of awards. It provides all HHS awarding agencies with a uniform set of minimum policy requirements that HHS staff must follow throughout a grant's life cycle.

The NIH Grants Policy Statement (GPS) provides NIH policy requirements that are incorporated into the terms and conditions of NIH awards. The NIH GPS has three parts that allow general information, application information, and other types of reference material to be separated from legally binding terms and conditions. EcoHealth's awards incorporate all requirements of the NIH GPS.

Requirements for Research Involving Enhanced Potential Pandemic Pathogens

On October 17, 2014, the White House announced that the Federal Government was instituting a governmentwide funding pause on gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, Middle East respiratory syndrome (MERS), or severe acute respiratory syndrome (SARS) viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.[6] On January 9, 2017, the White House issued *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO),* which described procedures for Federal agencies to adopt in order to lift the funding pause. The HHS *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* (HHS P3CO Framework), which was published on December 19, 2017, satisfied the January 9, 2017, White House guidance to address certain gain-of-function research and to lift the requirement for the research funding pause. The HHS P3CO Framework is intended to guide HHS funding decisions on research that is reasonably anticipated to create,

[5] 45 CFR §§ 75.351 through 75.353.

[6] Gain-of-function experiments aim to increase the ability of infectious agents by enhancing pathogenicity or increasing transmissibility. Accessed at https://obamawhitehouse.archives.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research on August 12, 2022.

transfer, or use enhanced potential pandemic pathogens (ePPPs).[7] NIH describes potential pandemic pathogens (PPPs) as bacteria, viruses, and other microorganisms that are likely highly transmissible, and capable of wide, uncontrollable spread in human populations, and highly virulent, making them likely to cause significant morbidity and/or mortality in humans. The HHS P3CO Framework includes criteria to guide funding decisions, roles, and responsibilities of HHS and awarding agencies, and related procedures. For example, one funding decision criterion states that "[t]he research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing Federal and institutional oversight of all aspects of the research throughout the course of the research."

In implementing the HHS P3CO Framework, NIH recognized that while ePPP research is inherently risky and requires strict oversight, the risk of not doing this type of research and not being prepared for the next pandemic is also high. NIAID implemented the HHS P3CO Framework by developing a standard operating procedure *NIAID Extramural Potential Pandemic Pathogen Care and Oversight (P3CO).* NIAID's P3CO risk assessment process begins with a review by program staff of all applications, proposals, supplements, and progress reports being considered for funding that involve research with a PPP. The NIAID Dual Use Research Concern (DURC)/P3CO Review Committee consists of NIAID program staff and leadership with broader infectious diseases and policy expertise who review research that could be subject to the HHS P3CO Framework. Based on the results of DURC/P3CO Review Committee meetings, NIAID would inform an applicant if it determined the applicant's research needs to undergo a departmental review under the HHS P3CO Framework. Appendix B lists requirements associated with reviewing research involving enhanced potential pandemic pathogens.

NIH Peer Review, Pre-Award, and Award Process for Grant Applications

Prior to an award being made, peer reviews are conducted by an initial review group or a scientific review group to evaluate scientific and technical merit.[8] Applications recommended for further consideration from the initial or scientific review groups receive a second level of review by an NIH Institute or Center's National Advisory Council or advisory board for scientific and technical merit and relevance to the Institute or Center's programs and priorities. Appendix C provides detailed information on the peer review process.

Following the peer review process, successful applications are reviewed by an Institute or Center's grants management and program officials for other considerations, including the project's budget, applicant eligibility, and an assessment of the applicant's management systems. NIH conducts final administrative reviews, including pre-award risk assessments. As

[7] The terms "gain-of-function" and "ePPP" were both used in Government guidance at different points during the audit period. While these terms may have some distinctions from a scientific perspective, for purposes of this audit, which does not assess the underlying science of the EcoHealth grants, we use the terms interchangeably. Both terms refer generally to research involving the enhancement of a pathogen's transmissibility or virulence.

[8] The scientific review group is composed primarily of non-Federal scientists who have expertise in the relevant scientific disciplines and current research areas.

part of a pre-award risk assessment, NIH's staff are instructed to ensure that concerns and recommendations found in the peer review process are addressed, and their results are documented in an Award Worksheet. Once an application is approved, the successful applicant receives a Notice of Award. Appendix D provides detailed information on the pre-award and award procedures.

HOW WE CONDUCTED THIS AUDIT

We obtained a list of all NIH awards to EcoHealth, and all subawards made by EcoHealth from FY 2014 through FY 2021 (audit period). Our audit covered three NIH awards to EcoHealth totaling approximately $8.0 million, which included $1.8 million of EcoHealth's subawards to eight subrecipients. See Table 1 for a list of grants included in the scope of our audit. Appendix E includes a detailed list of EcoHealth's NIH awards and subawards.

Table 1: Funding Awarded to and Spent by EcoHealth*

Award Number *(FYs Awarded)*	Award Title *(Subrecipients)*	Award Amount	Amount Spent
R01AI110964 *(FYs 2014–20)* *Initially awarded May 27, 2014*	Understanding the Risk of Bat Coronavirus Emergence *(Wuhan Institute of Virology; Wuhan University School of Public Health)*	$3,748,715	$3,376,503
U01AI151797 *(FYs 2020–21)* *Initially awarded June 17, 2020*	Understanding Risk of Zoonotic Virus Emergence in EID Hotspots of Southeast Asia *(Henry M. Jackson Foundation; Conservation Medicine; Chulalongkorn University; University of North Carolina at Chapel Hill)*	3,052,312	1,529,259
U01AI153420 *(FYs 2020–21)* *Initially awarded September 15, 2020*	Study of Nipah virus dynamics and genetics in its bat reservoir and of human exposure to NiV across Bangladesh to understand patterns of human outbreaks *(Institute of Epidemiology Disease Control and Research; International Centre For Diarrhoeal Disease Research, Bangladesh)*	1,155,842	478,971
Award and Expenditure Totals		**$7,956,869**	**$5,384,733**

* Grants awarded cover the audit period from FY 2014 through FY 2021. Grant expenditures are as of July 2021, the date for the latest available accounting records from EcoHealth at the time audit fieldwork began. Additional information about subawards can be found in Appendix E.

To address our first objective, our audit methodology was designed to assess NIH's policies, procedures, and internal controls in place to monitor the grant awards.[9] Specifically, we interviewed NIH and NIAID officials familiar with the grant award and monitoring process; reviewed HHS and NIH policies and procedures related to monitoring grant awards; reviewed email communications and other correspondence to gain insight on the types of interactions that occurred during the performance of the grant awards; reviewed Peer Review Summary Statements; reviewed required financial and programmatic reports; reviewed NIH oversight of EcoHealth's compliance with terms and conditions stated in the Notices of Award; and reviewed NIH's oversight and reporting requirements associated with ePPP. Our audit did not

[9] This audit was intended to focus on NIH's monitoring activities and did not fully assess the steps NIH took when awarding the grants.

assess the results of reviews by NIH to determine whether certain research involved gain-of-function or ePPP as this type of scientific examination was beyond the scope of this audit.

To address our second objective, our audit methodology was designed to assess EcoHealth's policies, procedures, and internal controls in place to manage and use grant funds. Specifically, we interviewed EcoHealth officials familiar with the grant awards and monitoring process; reviewed EcoHealth's policies and procedures; reviewed 12 of EcoHealth's subrecipient agreements covering 8 subrecipients; reviewed EcoHealth's subrecipient risk assessments; reviewed EcoHealth's subrecipient monitoring checklists; reviewed required financial and programmatic reports that EcoHealth submitted to NIH; and selected and reviewed 150 transactions totaling $2,578,567 across the 3 NIH awards comprised of different types of cost categories for allowability.

We conducted this performance audit in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Appendix A contains the details of our audit scope and methodology.

FINDINGS

In accordance with Federal requirements, NIH had policies and procedures in place for monitoring grant awards by reviewing financial and progress reports, taking action to implement enhanced monitoring for awards to EcoHealth, and reviewing research that could involve enhanced potential pandemic pathogens. However, NIH did not adequately monitor EcoHealth's grant awards in accordance with its policies and procedures and other Federal requirements. Specifically, NIH did not ensure EcoHealth in a timely manner submitted a progress report that was 2 years late and that NIH concluded contained evidence of a virus with growth that should have been reported immediately; did not ensure EcoHealth publicly reported required subaward data; and did not follow proper procedures to terminate an award to EcoHealth.

EcoHealth had procedures in place to conduct risk assessments of its subrecipients, and also had standardized checklists to document routine monitoring of its subrecipients. However, we found that EcoHealth did not ensure that subawards were compliant with Federal requirements, did not ensure compliance with subrecipient monitoring and reporting requirements, and did not comply with certain public disclosure requirements associated with reporting subaward funding. In addition, EcoHealth did not always use its grant funds in accordance with Federal requirements, resulting in $89,171 in unallowable costs. These deficiencies occurred because NIH and EcoHealth did not follow established policies and procedures.

Although NIH and EcoHealth had established monitoring procedures, lapses in complying with those procedures limited NIH and EcoHealth's ability to: (1) effectively monitor Federal grant awards and subawards to understand the nature of the research conducted, identify potential problem areas, and take corrective action; (2) provide the visibility and transparency to determine how these grant funds were used; and (3) mitigate the risk of noncompliance with Federal requirements and internal policies and procedures.

NIH HAD POLICIES AND PROCEDURES TO MONITOR GRANTS AND TO REVIEW FOR ENHANCED POTENTIAL PANDEMIC PATHOGENS

NIH established policies and procedures to monitor awards consistent with Federal requirements, which included implementing enhanced monitoring as a special award condition. NIH's policies and procedures addressed the October 2014 governmentwide pause on funding certain gain-of-function research and the subsequent HHS P3CO Framework requirements established in December 2017 to review research for enhanced potential pandemic pathogens.

The NIH GPS states that recipients are responsible for managing the day-to-day operations of grant-supported activities using their established controls and policies, as long as the controls and policies are consistent with NIH requirements. However, to fulfill their role to provide stewardship of Federal funds, NIH's awarding Institutes and Centers monitor their grants to identify potential problems and areas in which technical assistance to recipients might be necessary. This active monitoring is accomplished through reviews of reports and correspondence from the recipient, independent audit reports, site visits, and reviews of other information available to NIH. NIH's monitoring of a project or activity continues for as long as NIH retains a financial interest in the project or activity and may continue for a period of time after the grant is administratively closed out and NIH is no longer providing active grant support (NIH GPS, section 8.4).

GPAM requires that all monitoring be documented by NIH and that the Program and Grants Management Office (Program Office) at each Institute or Center must document the adequacy of recipient performance and compliance at least annually during the period of performance (Part H., Chapter 2, Par. 4). Furthermore, a Program Office's annual assessment should consist of a review, statement, and signed acknowledgment of the annual progress report. The statement should indicate the recipient's overall progress and whether there are known issues (Part H., Chapter 2, Par. 12). Finally, NIH does not have a direct relationship with subrecipients. The pass-through entity is responsible for monitoring its subrecipient's activities and compliance with terms and conditions of the award (Part H., Chapter 2, Pars. 15-16).[10]

[10] A pass-through entity is a non-Federal entity that provides a subaward to a subrecipient to carry out part of a Federal program.

NIH Had Established Policies and Procedures To Monitor EcoHealth's Awards

Consistent with the grant monitoring requirements outlined above, NIH's policies and procedures for monitoring awards primarily relied on reviewing reports and exchanging correspondence with the recipient. NIH uses various financial and progress reports that provide information about the amount of Federal funds spent, results from independent audit reports, and progress made on a grant award. In addition, we found that NIH had procedures in place to use information from the peer review process to identify specific grant-related concerns and develop award restrictions.

As an example, the peer review that was conducted prior to Year 1 of R01AI110964 noted concerns about the applicant's proposed research that were not fully addressed in the application. To minimize risk associated with the award, NIAID added restrictions to the Notice of Award that no human subjects may be involved in any project supported by the award until all requirements set forth by NIH for human subjects research had been met and approved by NIH, and that no funds for research involving human subjects may be drawn down until NIAID had notified EcoHealth that the issues had been resolved and the restriction removed. NIH was responsible for oversight to ensure compliance with these additional restrictions added to the Notice of Award.

NIH's Actions To Implement Enhanced Monitoring for Awards to EcoHealth

Consistent with Federal requirements, NIH imposed specific award conditions to perform enhanced monitoring on two EcoHealth awards, U01AI151797 and U01AI153420, based on NIH's belief that EcoHealth did not properly monitor WIV's activities in compliance with grant requirements. Federal regulations at 45 CFR § 75.371 allow for HHS awarding agencies to impose additional award conditions as described in 45 CFR § 75.207 as a remedy for noncompliance with terms and conditions of a Federal award. Federal regulations (45 CFR § 75.207) allow for HHS awarding agencies to impose specific award conditions as needed when an applicant or recipient has a history of failing to comply with general or specific terms and conditions of a Federal award, when an applicant or recipient fails to meet expected performance goals, or when an applicant is not otherwise responsible. These additional award conditions include but are not limited to requiring additional, more descriptive financial reports and requiring additional project monitoring.

Below we describe a sequence of events that culminated in NIH implementing enhanced monitoring by imposing specific award conditions for its U01AI151797 and U01AI153420 awards to EcoHealth.[11]

- April 24, 2020: NIH terminated the R01AI110964 award originally awarded in 2014.

[11] These events represent actions taken by NIH and are not intended to be all-encompassing of NIH's enhanced monitoring of EcoHealth.

- June 17, 2020: NIH awarded new funds to EcoHealth to study the Risk of Zoonotic Virus Emergence in Southeast Asia (Grant Number U01AI151797).

- July 8, 2020: NIH reinstated and immediately suspended the R01AI110964 award via a letter with this date to EcoHealth.

- August 28, 2020: NIH revised the terms and conditions of award U01AI151797 to require EcoHealth to submit to NIH copies of all subrecipient agreements established under the award and documentation of timely entries of subrecipient information pursuant to Federal Funding Accountability and Transparency Act of 2006 (FFATA) requirements.

- September 15, 2020: NIH awarded new funds to EcoHealth to study the Nipah virus in Bangladesh (Grant Number U01AI153420).

- October 23, 2020: NIH acknowledged receipt of EcoHealth's appeal of the grant suspension dated August 13, 2020, related to R01AI110964; reiterated requests for materials, information, and a site visit by an outside inspection team made in the July 8, 2020, letter to EcoHealth; and further requested from EcoHealth copies of WIV subrecipient agreements, risk assessments, and biosafety reports.

- April 13, 2021: NIH acknowledged receipt of EcoHealth's April 11, 2021, response to NIH's July 8, 2020, and October 23, 2020, letters, and reiterated certain requests made on October 23, 2020.

- July 23, 2021: NIH wrote to inform EcoHealth that the Year 5 progress report for R01AI110964, which was due in September 2019, was late. NIH also requested subrecipient agreements, audit reports, safety monitoring documents, progress reports, and financial records for both the U01AI151797 and U01AI153420 awards.

- January 6, 2022: NIH wrote to inform EcoHealth that it was adding specific award conditions on the awards that were first issued in June and September 2020 due to a history of failure to comply with several elements of the terms and conditions of grant awards and required EcoHealth to develop a Corrective Action Plan for both U01AI151797 and U01AI153420.

NIH's Monitoring of EcoHealth Grant Awards Included Reviews for Enhanced Potential Pandemic Pathogens

NIAID had processes related to assessing and monitoring awards potentially involving ePPP. During the scope of our audit, NIAID's processes included assessing whether research was subject to the gain-of-function funding pause (from 2014–17) or subject to the HHS P3CO Framework review (after 2017). As described in more detail in subsequent paragraphs, NIAID

reviewed award R01AI110964 to EcoHealth after the gain-of-function funding pause was in effect to assess whether it was subject to the pause, and NIH determined that the R01AI110964 research was not subject to the gain-of-function funding pause. After the gain-of-function funding pause was lifted in 2017, NIH assessed all three awards that were initiated or ongoing to determine whether to refer research for review under the HHS P3CO Framework. NIH did not refer any of the three awards to the Department for review under the HHS P3CO Framework. Our audit did not review the basis of NIH's determinations, which is a scientific issue beyond our scope and expertise, and we do not make any conclusions about NIH's determinations about gain-of-function research or the necessity of a departmental review under the HHS P3CO Framework. However, we note that NIH recognized the need for strict oversight of research involving ePPP. NIAID's P3CO standard operating procedure instructed program staff reviewing proposed research involving a PPP to "err on the side of inclusion" when determining whether proposed research should be referred to the NIAID DURC/P3CO Committee for further review and possible referral to the Department for review under the HHS P3CO Framework.

The following discussion lays out in greater detail conditions and requirements for each grant related to ePPP. It was NIH's responsibility to monitor EcoHealth's compliance with these requirements described below.

Grant Number R01AI110964

On May 28, 2016, the NIAID Grants Management Specialist and Program Officer for the grant notified EcoHealth that, based upon information in the progress report for Year 2 submitted by EcoHealth on May 13, 2016, NIAID had determined that the research could be gain-of-function and subject to the funding pause on certain gain-of-function research. NIAID stated that, per the funding pause announcement, new funding would not be released for gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity or transmissibility in mammals via the respiratory route. The letter requested additional information from EcoHealth about the research including support as to whether the research did or did not include work applicable to the gain-of-function funding pause.

On June 8, 2016, EcoHealth provided a response with additional details describing the R01AI110964 research. In that letter, EcoHealth explained the goal of the proposed work was to understand the potential origins of MERS-Coronavirus (CoV) in bats by studying bat MERS-like CoVs in detail. EcoHealth stated that it was highly unlikely that this work would have any pathogenic potential. EcoHealth's letter did state that should any of these recombinants show evidence of enhanced virus growth greater than certain specified benchmarks involving log growth increases, or grow more efficiently in human airway epithelial cells, EcoHealth would immediately: (1) stop all experiments with the mutant, (2) inform the NIAID Program

Officer of these results, and (3) participate in decision-making trees to decide appropriate paths forward.[12]

On July 7, 2016, NIAID officials responded to EcoHealth saying that they had reviewed the original grant application and the documents and explanations provided by EcoHealth in response to NIAID's question about whether the research included any gain-of-function work subject to the funding pause. NIAID determined that the work proposed to generate MERS-like or SARS-like chimeric coronaviruses was not subject to the gain-of-function research funding pause and was not reasonably anticipated to have enhanced pathogenicity or transmissibility in mammals via the respiratory route. Furthermore, NIAID stated that if any of the MERS-like or SARS-like chimeras generated under this grant showed evidence of enhanced virus growth greater than certain specified benchmarks involving log growth increases, EcoHealth would immediately stop all experiments with these viruses and provide the NIAID Program Officer and Grants Management Specialist with the relevant data and information related to these unanticipated outcomes.[13, 14]

On July 5, 2018, the NIAID Grants Management Specialist and Program Officer sent EcoHealth a letter introducing the HHS P3CO Framework published in December 2017. In response to the HHS P3CO Framework, NIAID re-reviewed EcoHealth's R01AI110964 grant application and other information provided by EcoHealth and determined that the experiments to generate MERS-like or SARS-like chimeric coronaviruses were not subject to the HHS P3CO Framework. However, also in 2018, NIAID revised the terms and conditions of the Year 5 award to indicate that should experiments proposed in this award result in a virus with enhanced growth by more than certain specified benchmarks involving log growth increases, EcoHealth must notify NIAID immediately, and further research may require review by HHS according to the HHS P3CO Framework. Further information about events occurring related to the Year 5 award are described in the audit findings section related to the failure of EcoHealth to submit a progress report on time.

[12] The agenda for NIAID's weekly DURC/Gain-of-Function meeting scheduled for June 17, 2016, included a discussion item related to the R01AI110964 award and whether the research supported under the award was subject to the gain-of-function funding pause.

[13] Although the letter had an immediate notification requirement, as we describe later in this report, we did not find evidence that NIAID clearly defined expectations as to the process and timeline EcoHealth should follow to provide "immediate notification."

[14] NIH incorporated restrictions described in the July 7, 2016, letter in the Notice of Award issued on July 22, 2016. The Notice of Award stated no funds are provided and no funds can be used to support gain-of-function research covered under the October 17, 2014, White House announcement.

Grant Number U01AI151797

Grant U01AI151797 was awarded after implementation of the HHS P3CO Framework. NIAID did not refer this grant to the DURC/P3CO Committee for consideration on the need for a departmental review under the HHS P3CO Framework. The following events provide details regarding this decision.

- On April 30, 2020, during the application review process, NIAID staff internally noted a reference to possible enhanced potential pandemic pathogens and took additional steps to review the proposed research as required by the HHS P3CO Framework.

- On May 1, 2020, NIAID staff requested additional information from EcoHealth regarding the nature of experiments related to this award.

- On May 5, 2020, EcoHealth responded to the request outlining two approaches to the research.

- On May 7, 2020, during an internal review of this additional information, NIAID staff noted that no further action was needed as the proposed research did not meet the criteria for classification as P3CO studies based on a review of the application and additional information from EcoHealth. However, NIAID staff noted there was a possibility that this may change in the future, and suggested adding a special P3CO term of award, which we further describe in the next bullet.

- On June 17, 2020, NIAID issued the Notice of Award and addressed the possible P3CO concern noted on May 7, 2020, by requiring EcoHealth to immediately stop work on all experiments and notify the NIAID Program Officer and Grants Management Specialist should any experiments proposed in the application result in specific outcomes. Furthermore, the award stated that it does not include funds to support research subject to the HHS P3CO Framework.

Grant Number U01AI153420

In response to our request for steps taken for this grant application and possible review under the HHS P3CO Framework, NIAID informed OIG that it had reviewed and determined the application did not meet the scope of the HHS P3CO Framework, noting that sufficient information was provided in the grant application to review the proposed experiments and use of pathogens. NIAID did not provide OIG with any further documentation indicating that it considered referring the research to the Department for review under the HHS P3CO Framework.

NIH'S MONITORING OF ECOHEALTH GRANT AWARDS DID NOT COMPLY WITH HHS POLICIES AND PROCEDURES AND FEDERAL REQUIREMENTS

NIH Did Not Ensure a Progress Report Was Submitted in a Timely Manner for One of EcoHealth's Grant Awards

Contrary to GPAM requirements, NIH did not follow up in a timely manner with EcoHealth after it failed to submit a progress report due September 2019. EcoHealth's failure to submit a progress report in a timely manner and NIH's failure to follow up on a missing progress report limited NIH's ability to effectively monitor its grant award to EcoHealth and evaluate whether the special terms and conditions were met. This oversight failure is particularly concerning because NIH had previously raised concerns with EcoHealth about the nature of the research being performed. Once NIH received and reviewed the late progress report, NIH concluded the research resulted in a virus with enhanced growth. EcoHealth's Notice of Award for Year 5 of R01AI110964 was issued on June 18, 2018. It had a budget period of June 1, 2018, to May 31, 2019. The Notice of Award required that a final progress report be submitted within 120 days of the budget period's end date. Thus, EcoHealth should have submitted its progress report for Year 5 by the end of September 2019.

Completing an online progress report is a multistep process.[15] The principal investigator or delegate initiates the progress report. Processing of the progress report continues with edits, and in the final step the progress report is submitted to NIH. Until the progress report is submitted to NIH, the online system marks the report status as "draft" and the submission date space is blank. We found evidence in the online system that EcoHealth initiated the progress report in July 2019; however, not until after NIH requested the progress report in July 2021 did EcoHealth submit it on August 3, 2021, nearly 2 years late.

While EcoHealth bears responsibility for its late progress report, which we discuss in more detail later in this report, we find no evidence that NIH informed EcoHealth of the late progress report from the time EcoHealth initiated the report in NIH's online system until July 2021, just short of 2 years after the progress report was initially due. Furthermore, NIH did not comply with the GPAM requirement to follow up with EcoHealth about the late report no later than 30 days after the established due date (Part H., Chapter 2, Par. 45).[16] NIH's failure to follow up with EcoHealth about the late progress report limited its ability to understand the nature of the research conducted during Year 5 of the award on a timely basis.

Below we provide an overview of NIH's and EcoHealth's interpretations of Year 5's research results. We again note that our audit did not assess scientific results for any of the experiments

[15] The online system is described in Appendix D.

[16] As we describe later in this report, this action was taken after NIH terminated, reinstated, and suspended the award.

or make any determination regarding the accuracy of NIH's or EcoHealth's interpretations of Year 5's research results.

EcoHealth's Notice of Award for Year 5 of R01AI110964 required EcoHealth to immediately notify its NIAID Program Officer and Grants Management Specialist if any experiments proposed in the award resulted in a virus with enhanced growth by more than one log compared to wild-type strains. The Notice of Award also stated that research involving the resulting virus(es) may require review under the HHS P3CO Framework.

According to NIH's evaluation of EcoHealth's progress report for Year 5 of the grant, NIH believed there was evidence that the research conducted by EcoHealth's subrecipient WIV during Year 5 resulted in enhanced growth by more than one log, thus triggering the special term and condition to immediately notify NIAID and potentially requiring the research to undergo review under the HHS P3CO Framework. NIH required immediate notification of this type of unexpected research result, because a one-log increase in growth has been used as a criteria for initiating a secondary review to determine whether the research aims should be evaluated or new biosafety measures should be enacted.

With respect to the issue of the special term and condition to provide "immediate notification" to NIAID, EcoHealth asserted that the experiment reported in the Year 5 progress report included results from a followup analysis of the same experiment conducted in Year 4 of the award and reported in the Year 4 progress report. However, based on NIH's Office of Extramural Research review of the progress reports for Year 4 and Year 5, NIH explained that it cannot determine whether Year 4's progress report included results from the same experiment.[17] EcoHealth believes it was in compliance with the requirement to immediately notify NIAID of the research results because EcoHealth reported the results in the Year 4 progress report. However, NIH does not believe reporting research in a progress report constitutes immediate notification. We agree with NIH's assessment that reporting research in a progress report does not constitute immediate notification; however, we did not find evidence that NIH clearly defined requirements related to the process and timeline EcoHealth should follow to provide immediate notification.

NIH Did Not Ensure EcoHealth Reported Required Subaward Data for Award R01AI110964

NIH's monitoring did not discover EcoHealth's noncompliance with requirements to report subawards for more than 5 years, which demonstrates that NIH's policies and procedures were not always effective. FFATA as amended requires most recipients of Federal funds awarded on or after October 1, 2010, to report on subawards and subcontracts equal to or greater than $25,000. Recipients use the FFATA Subawarding Reporting System (FSRS) to report their

[17] While NIH was not able to substantiate whether the Year 4 and Year 5 experiments were the same, NIH informed us that it does not believe that either experiment described is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or the COVID-19 pandemic.

subawards. Prior to July 2020, EcoHealth had not complied with the subaward reporting requirement for at least 5 years. Not reporting required subaward information limits NIH and the general public's visibility into, and transparency of, how these grant funds were used. While EcoHealth was not in compliance with the disclosure requirements, it was not evident that NIH was aware of this failure until July 2020, when NIH required EcoHealth to comply with the disclosure requirements as one of the conditions of its grant suspension. Given that EcoHealth's first subaward covered the period June 1, 2014, through May 31, 2015, we believe NIH's monitoring of EcoHealth's grants should have revealed EcoHealth's failure to comply with the subaward disclosure requirement as early as 2016 during the renewal process for Year 3 of the award.

As part of its monitoring, NIH has access to recipient audit reports and financial statements. Based on our review of audit reports, we noted that EcoHealth's Schedule of Expenditures of Federal Awards (SEFA) included in its financial statements for the years ended June 30, 2016, June 30, 2017, June 30, 2018, and June 30, 2019, did not include the proper amounts of subaward funding for NIAID's Federal programs.[18] We would reasonably expect NIH's monitoring activities to detect this repeated reporting omission and then for NIH to advise EcoHealth to modify that section of its financial statements.

NIH Did Not Follow All Required Procedures To Terminate One of Its Grant Awards

Although NIH found EcoHealth to have several instances of noncompliance with award requirements, NIH did not follow Federal regulations and departmental policy to appropriately terminate one of EcoHealth's awards.

As part of NIH's monitoring of the R01AI110964 award to EcoHealth, NIH sent a letter to EcoHealth on April 19, 2020, requiring EcoHealth to cease providing any funds to its subrecipient WIV, citing concerns that WIV may have been involved with the release of the coronavirus responsible for COVID-19. On April 21, 2020, EcoHealth responded that it would comply with this request. Three days later, on April 24, 2020, NIH sent a letter informing EcoHealth that it was terminating the grant "for convenience," stating NIH did not believe the current project outcomes aligned with program goals and agency priorities.

We found several deficiencies with the notice NIH provided to EcoHealth terminating the award:

- NIH stated that it did not believe the current project outcomes aligned with program goals and agency priorities. Accordingly, the termination notice cited "for convenience" as the cause for termination; however, that is not a valid termination cause pursuant to

[18] As part of a grant recipient's financial statements, a recipient of a Federal grant award must prepare a SEFA that covers the period of the financial statements to disclose the total amount of a Federal award spent, subawards received, and amounts passed through to subrecipients.

45 CFR § 75.372.[19]

- The termination notice did not include a statement of EcoHealth's appeal rights as required by Federal regulations and NIH GPS.[20]

- There was no NIH official named on the termination notice to whom EcoHealth should submit an appeal, as required by NIH GPS.[21]

- The termination notice did not provide any sort of opportunity for EcoHealth to provide information and documentation challenging the termination action, as required by Federal regulations.[22]

On May 22, 2020, EcoHealth submitted a formal appeal to NIH, challenging the termination action. In absence of a specific person at NIH named on the termination notice to send an appeal to, EcoHealth addressed its appeal to the NIH Deputy Director for Extramural Research who signed the termination letter.

On July 8, 2020, NIH wrote to EcoHealth informing EcoHealth that NIH had withdrawn its termination of grant R01AI110964 and reinstated the grant. The letter went on to cite that NIH had received reports that WIV, one of EcoHealth's subrecipients, had been conducting research at WIV's facilities in China that posed serious biosafety concerns and, as a result, created health and welfare threats to the public in China and other countries. In this letter, NIH proceeded to suspend all activities related to R01AI110964 until concerns listed in the letter were addressed to NIH's satisfaction.[23] The notice cited that the suspension was taken in accord with 45 CFR § 75.371 and that the action was not appealable; however, EcoHealth could provide information and documentation demonstrating that WIV and EcoHealth had satisfied certain requirements.

GPAM (Part H, Chapter 4, Par. 21) states that the notice of post-award suspension of award activities must clearly indicate which corrective actions must occur during the enforcement action and an HHS operating division's intent to terminate the award if the recipient does not meet the conditions of the enforcement action.

[19] Appendix F contains Federal requirements associated with terminating and suspending grant awards.

[20] 45 CFR § 75.374(a) and NIH GPS, Section 8.7.

[21] NIH GPS, section 8.7.

[22] 45 CFR § 75.374(a).

[23] EcoHealth was to address certain items related to lab safety and oversight of WIV. During the period of suspension, EcoHealth was not to allow any research to be conducted under the suspended award, nor spend any grant funds associated with the suspended award.

NIH and EcoHealth had ongoing communications spanning a more than 2-year period addressing items related to the grant suspension. Most recently, on August 19, 2022, NIH sent a letter notifying EcoHealth of actions: (1) to terminate the subaward from EcoHealth to WIV; (2) to explore renegotiating the remainder of the award without involvement from WIV, and without a significant scientific departure from the original peer-reviewed project; and (3) if the remaining award could be renegotiated, to issue a revised award subject to specific award conditions. NIH noted that a partial termination is appealable. Because of these actions, we make no recommendations to NIH related to its initial termination of the R01AI110964 award to EcoHealth.

ECOHEALTH HAD POLICIES AND PROCEDURES TO MANAGE GRANT AWARDS AND MITIGATE POTENTIAL RISK BEFORE SUBAWARDING GRANT FUNDS

EcoHealth had policies and procedures to manage grant awards and mitigate potential risk before subawarding grant funds as we describe below. EcoHealth is responsible for the oversight of the operations of Federal award-supported activities and must monitor subrecipient activities under Federal awards to assure compliance with applicable Federal requirements and performance expectations are being achieved (45 CFR § 75.342(a)). In addition, in its role as a pass-through entity, EcoHealth must evaluate each subrecipient's risk of noncompliance with Federal statutes, regulations, and the terms and conditions of the subaward to determine the appropriate subrecipient monitoring.[24]

This risk assessment may consider factors such as:

- the subrecipient's prior experience with the same or similar subawards,
- the results of previous audits,
- whether the subrecipient has new personnel or new or substantially changed systems, and
- the extent and results of HHS awarding agency monitoring (e.g., whether the subrecipient also receives Federal awards directly from an HHS grant-awarding agency).

In February 2017, EcoHealth established a policy documenting its responsibility for monitoring the programmatic and financial activities of its subrecipients to ensure proper stewardship of sponsor funds to comply with the requirements of 45 CFR part 75. Among other things, the policy requires EcoHealth to monitor programmatic progress and the ability of the subrecipient to meet the objectives of the subaward, to complete risk assessments on new subrecipient organizations, and to conduct annual assessments on active subrecipient organizations. EcoHealth uses a risk-based approach to subrecipient monitoring, focusing on those

[24] 45 CFR § 75.352(b).

subrecipients deemed at greatest risk for noncompliance. See Table 2 for criteria EcoHealth used for assigning a level of risk.

Table 2: Factors for Assigning Level of Risk

- foreign versus domestic[25]
- maturity of organization
- subrecipient's prior experience with similar subawards or awarding agency
- adequacy of facilities[26]
- percentage of award passed through to subrecipient
- subrecipient familiarity with award mechanism
- audit results
- accounting/procurement systems
- scope of work and project deliverables
- familiarity of EcoHealth and subrecipient principal investigators
- rate of subrecipient spending on award
- subrecipient organization type

EcoHealth's risk analysis process included:

- checking the General Services Administration (GSA) System for Award Management (SAM) website to determine whether the subrecipient was suspended or debarred,

- verifying that the subrecipient had a compliant conflict of interest policy if required by the awarding agency, and

- verifying that the subrecipient maintained an adequate financial management system to account for award funds.

Based on our review of documentation that EcoHealth provided OIG, we found that EcoHealth officials met with WIV staff in person on at least 20 occasions between June 2014 and December 2019 and traveled to Wuhan, China, to meet with individuals from WIV at least annually during that time to discuss the research conducted under its subaward.[27] EcoHealth staff told OIG that they engaged in frequent phone calls and email exchanges with WIV staff throughout the grant period until the time the grant was terminated in April 2020.

Furthermore, since EcoHealth implemented its subrecipient monitoring policy in February 2017, we found that EcoHealth conducted risk assessments for each of its subrecipients. EcoHealth

[25] According to EcoHealth's risk checklist, foreign organizations are rated with "medium" or "high" risk, depending on the stability of the country's government and financial system.

[26] According to EcoHealth's risk checklist, this refers to whether the facilities are adequate and well-established; adequate and new; or inadequate.

[27] The documentation indicated that some meetings were at WIV.

also completed monitoring checklists for those subrecipients and conducted desk audits for selected subrecipients. Due to the COVID-19 pandemic, EcoHealth told OIG it had not conducted any in-person site visits at any of its subrecipients' facilities from January 2020 through the end of audit fieldwork in August 2022.

ECOHEALTH DID NOT ENSURE SUBAWARDS WERE COMPLIANT WITH FEDERAL REQUIREMENTS

Subaward Agreements Did Not Contain All Required Information

Contrary to Federal regulations, none of the subaward agreements contained all of the required information. Pursuant to 45 CFR § 75.352(a), each pass-through entity such as EcoHealth must ensure that each subaward is clearly identified as a subaward and must include specific information on the subrecipient agreement.[28]

Of the 11 subrecipient agreements we reviewed that EcoHealth used to subaward funding, all 11 agreements lacked at least 1 of these required elements.[29] This occurred because EcoHealth's policies and procedures did not ensure that the required data elements were included on each subaward. EcoHealth's noncompliance with these requirements limited the transparency of key Federal funding information to the subrecipients, such as the total amount of a Federal award committed to a subrecipient and the Federal award identification number. See Appendix H for details about subrecipient agreements lacking required data elements.

Inaccurate Subrecipient and Consultant Agreements

Some of the subrecipient and consultant agreements we reviewed were not written according to Federal regulations, which require non-Federal entities to maintain a financial management system that provides for the following:

- accurate, current, and complete disclosure of the financial results of each Federal award or program; and

- records that adequately identify sources and applications of funds for federally funded activities (45 CFR § 75.302(b)).

During our review of subrecipient and consultant agreements, we identified six agreements that contained inaccurate references to funding sources in EcoHealth's financial management system. In some cases, these incorrect references were in the form of unique grant identifiers in the accounting system; in other cases, written text in the agreement described a different funding source. According to EcoHealth, these errors occurred during copying and pasting of

[28] Appendix G contains a list of requirements associated with subrecipient agreements and monitoring.

[29] We also reviewed an additional subrecipient agreement, but it was not subject to these requirements because the agreement was signed prior to implementation of the requirements at 45 CFR § 75.352(a).

information from old agreements to new agreements. While we did not find evidence that the wrong funding source was used to pay subrecipients or consultants, it is possible that not all of EcoHealth's subrecipients or consultants were fully informed about the Federal funding source associated with their funding.

ECOHEALTH DID NOT ENSURE COMPLIANCE WITH REPORTING AND SUBRECIPIENT MONITORING REQUIREMENTS

The Progress Report Was Not Submitted in a Timely Manner for Year 5 of a Grant Award

As we described earlier in this report, EcoHealth submitted its Year 5 progress report late and the report involved research that NIH believed resulted in a virus with enhanced growth. EcoHealth's Notice of Award for Year 5 of R01AI110964 was issued on June 18, 2018. It had a budget period of June 1, 2018, to May 31, 2019. The Notice of Award required a final progress report be submitted within 120 days of the budget period's end date. Thus, EcoHealth should have submitted its progress report for Year 5 by the end of September 2019. We found evidence in the online system used to submit progress reports that EcoHealth initiated the progress report in July 2019; however, not until after NIH requested the progress report in July 2021 did EcoHealth submit the progress report on August 3, 2021, nearly 2 years late.

EcoHealth claimed that it had difficulty accessing the system used to submit progress reports, but we could not find evidence to support that claim. While we found that EcoHealth contacted NIH in late July 2019 in reference to the progress report, we did not find evidence that EcoHealth notified NIH about difficulty accessing the system used to submit progress reports. Furthermore, we found no evidence that NIH requested the progress report until July 2021. Due to late submission of the Year 5 progress report, EcoHealth was not in compliance with the report submission deadlines, which contributed to NIH not being made aware of the research results and not having information needed to understand the nature of research conducted in a timely manner.

EcoHealth Was Unable To Obtain Scientific Documentation From a Subrecipient

EcoHealth has been unable to provide NIH with certain scientific documentation in response to an NIH request. Federal regulations (45 CFR § 75.364(a)) require non-Federal entities to grant access to any documents, papers, or other records of the non-Federal entity that are pertinent to the Federal award to the HHS awarding agency, the Inspector General, or the pass-through entity. EcoHealth's subaward agreements state that EcoHealth may examine, audit, or have audited the records of the subrecipient as they relate to activities supported by the agreement.

On November 5, 2021, NIH requested that EcoHealth provide certain scientific documentation from WIV substantiating research covering EcoHealth's Year 4 (project period June 1, 2017, to May 31, 2018) and Year 5 (project period June 1, 2018, to May 31, 2019) progress reports to

gain insights into the nature of the experiments that were performed.[30] In turn, EcoHealth requested the information from WIV. However, based on records reviewed, we did not see evidence that EcoHealth obtained the scientific documentation. EcoHealth officials confirmed to us that WIV had not been responsive to its request to provide the scientific documentation and indicated it was unlikely to receive the requested information. As a result, EcoHealth has been unable to comply with NIH's request on this matter. In a discussion of this specific matter with NIH's Deputy Director for Extramural Research, NIH acknowledged to OIG that WIV may never provide EcoHealth with the requested documentation. Although EcoHealth's subaward agreements had language permitting it to access the records of its subrecipients and also had policies and procedures to assess and monitor its subrecipients, EcoHealth has been limited in its ability to require WIV to take specific action or provide specific information. This has been due in part to the lack of cooperation by WIV, as reported by EcoHealth and NIH.

The approach in the governmentwide regulations that NIH follows related to oversight and monitoring of foreign subrecipients also contributed to this finding. These regulations are designed to have a prime grant recipient monitor the activities of a subrecipient, rather than requiring the grant-awarding agency—in this case, NIH—to conduct active monitoring of subrecipients. NIH expects its prime grant recipients to be accountable for performance of the research project, and it also expects prime grant recipients to address and report certain problems with its subrecipients to NIH—sometimes immediately. For foreign subrecipients, the effectiveness of the prime recipient's monitoring relies on the level of cooperation between the recipient and the subrecipient. In certain countries in which the research is performed, there may be a risk that larger political or governmental issues may impede cooperation and prime recipients will have limited ability to effectively monitor their foreign subrecipients.

As previously stated in this report, OIG has identified NIH's oversight of grants to foreign applicants as a potential risk to the Department in meeting program goals and the appropriate use of Federal funds. Additionally, prior OIG work has found foreign recipients at risk of noncompliance with grant requirements and maintaining documentation that is needed to effectively oversee and manage Federal grant awards.[31]

EcoHealth Did Not Comply With Certain Requirements Associated With Reporting Subaward Funding

Contrary to Federal regulations, EcoHealth did not properly report subawards in its SEFA or report them on the FSRS website. Regulations at 45 CFR § 75.510(b) require auditees to prepare a SEFA for the period covered by the auditee's financial statements. The SEFA must

[30] The scientific documentation requested consisted of complete and dated copies of the original laboratory notebook entries and original electronic files that led to the Year 4 and Year 5 progress reports.

[31] *Although CDC Implemented Corrective Actions To Improve Oversight of the President's Emergency Plan for AIDS Relief Recipients, Some Internal Control Weaknesses Remained*, A-04-18-01010, December 2020, available at https://oig.hhs.gov/oas/reports/region4/41801010.asp.

include the total Federal awards expended. Regulations at 45 CFR §§ 75.510(b)(2-4) require the recipient to list the name of each pass-through entity for which it received Federal subawarded funding and require the auditee to include the total amount provided to subrecipients from each Federal program.

The SEFA in EcoHealth's financial statements for the years ended June 30, 2016, June 30, 2017, June 30, 2018, and June 30, 2019, did not include the proper amount of subawarded funding for NIAID's Federal programs. EcoHealth stated that its independent accountants advised EcoHealth not to include that information; however, this advice was contrary to Federal reporting requirements. In addition, EcoHealth's failure to report the subaward funding limited NIH's access to accurate information in the audit report's SEFA to use in NIH's monitoring process.

FFATA requires most recipients of Federal funds awarded on or after October 1, 2010, to report on subawards and subcontracts equal to or greater than $25,000. Recipients use FSRS to report their subawards. Prior to July 2020, EcoHealth had not complied with the reporting requirement to report its subawards. Until NIH informed EcoHealth in July 2020 that it was not in compliance with these reporting requirements for its subawards, EcoHealth did not report any of its subawards on the FSRS website according to Federal requirements. During the audit, we noted EcoHealth did not have sufficient policies and procedures to address these reporting requirements.

ECOHEALTH DID NOT ALWAYS USE ITS GRANT FUNDS ACCORDING TO FEDERAL REQUIREMENTS

We determined that EcoHealth claimed $89,171 in costs that did not meet Federal requirements. These costs included salaries exceeding the NIH salary cap, employee bonuses, travel costs, tuition costs, indirect costs claimed by a subrecipient, other costs, and associated fringe and indirect costs. See Table 3 for a summary of unallowable costs by cost category.

Table 3: Summary of Unallowable Costs by Cost Category

Cost Category (Associated Grant Numbers)	Unallowable Direct Cost	Unallowable Fringe Benefit and Indirect Cost	Total Unallowable Cost
Salaries and Bonuses (All Grant Numbers)	$26,604*	$17,836	$44,440
Tuition (R01AI110964)	13,951	4,641	18,592
Indirect Costs Claimed by Subrecipient (R01AI110964)	13,037	0	13,037
Travel (R01AI110964)	5,752	1,876	7,628
Other (R01AI110964 and U01AI151797)	4,571	903	5,474
Unallowable Cost Totals	**$63,915**	**$25,256**	**$89,171**

* This amount includes $10,627 and $15,977 in unallowable salary and bonus costs, respectively.

Federal regulations at 45 CFR § 75.403 require that costs:

- be necessary and reasonable for the performance of the Federal award and be allocable under these principles,
- conform to any limitations or exclusions set forth in these principles or in the Federal award,
- be consistent with policies and procedures that apply uniformly to both federally financed activities and other activities of the non-Federal entity, and
- be adequately documented.

Salary Costs Exceeded the NIH Salary Cap

We determined that $10,627 in sampled salary costs for selected EcoHealth employees were claimed in excess of the NIH salary cap. NIH funds shall not be used to pay the salary of an individual through a grant or other extramural mechanism at a rate in excess of that prescribed. Applications and proposals with categorical, direct-cost budgets reflecting direct salaries of individuals in excess of the rate prescribed are to be adjusted according to the legislative salary limitation (NIH GPS, section 4.2.10). For our audit period, NIH's salary cap ranged from $181,500 to $199,300 for recipient employees fully allocated to NIH grant awards. For recipient

employees whose salaries are partially funded by NIH grant awards, the salary cap is adjusted proportionally to the amount of effort charged to the NIH award.

While EcoHealth indicated that it was aware of the NIH salary cap and properly accounted for it, we determined that EcoHealth did not consider the percent of effort assigned to the grant, resulting in amounts paid with NIH grant funds in excess of the salary cap.

EcoHealth Provided Employee Bonuses Without an Established Plan and Claimed Unallowable Indirect and Fringe Benefits

We identified $15,977 in employee bonuses that were improperly paid with NIH grant funds to seven EcoHealth employees. The bonuses paid were not in accordance with NIH GPS requirements. The NIH GPS states that "Incentive compensation to employees based on cost reduction, or efficient performance, suggestion awards, safety awards, etc., is allowable to the extent that the overall compensation is determined to be reasonable and such costs are paid or accrued pursuant to an agreement entered into in good faith between the non-Federal entity and the employees before the services were rendered, or pursuant to an established plan followed by the non-Federal entity so consistently as to imply, in effect, an agreement to make such payment." (NIH GPS, section 7.9.1)

EcoHealth's policy on Performance Management states that positive performance evaluations do not guarantee increases in salary, bonus payments, or any other type of discretionary compensation. Promotions, salary increases, and discretionary payments of any kind are solely under the discretion of management and depend upon many factors in addition to individual performance (EcoHealth Employee Handbook, chapter 19).

We determined that all $15,977 in bonuses we reviewed were unallowable because there was no agreement entered into between EcoHealth and the employees before the services were rendered. Nor do we believe the language in EcoHealth's Employee Handbook meets the requirements listed in NIH GPS as it relates to having an established plan to pay bonuses. The language in EcoHealth's Employee Handbook is too vague to be an agreement to make a bonus payment or an established plan that is followed so consistently as to imply an agreement to make a bonus payment. EcoHealth believed that charging employee bonuses to NIH grants was allowable.

In addition to the unallowable salary costs in excess of NIH's salary cap and unallowable bonus costs, we determined that associated indirect and fringe benefit costs that EcoHealth paid with NIH grant funds of $17,836 were also unallowable.

Tuition Costs Did Not Meet Federal Requirements

We determined that EcoHealth claimed unallowable Ph.D. education tuition costs for an EcoHealth employee enrolled at Kingston University, located in London, England. The claims were made to the R01AI110964 research grant in the amounts of $4,603 and $9,348 for the

2018–19 and 2019–20 academic years, respectively. Regulations at 45 CFR § 75.472 specifically allow for the cost of training and education provided for employee development. However, section 7.9.1 of NIH GPS states that trainee costs are allowable only under predoctoral and postdoctoral training grants.

EcoHealth explained that it believed paying tuition costs with NIH grant funds was allowable. According to the NIH GPS, that is true only in limited cases involving a specific type of NIH grant award, and EcoHealth's grant was not of this limited type. Accordingly, we identified a total of $13,951 in unallowable tuition costs, along with $4,641 in associated indirect costs.

Indirect Costs Were Claimed in Excess of Allowable Rates for Foreign Subawards

We determined that EcoHealth claimed $13,037 in unallowable indirect costs associated with subawards at WIV. Facilities and administrative costs under grants to foreign and international organizations will be funded at a fixed rate of 8 percent of modified total direct costs, exclusive of tuition and related fees, direct expenditures for equipment, and subawards in excess of $25,000. These funds are paid to support the costs of compliance with Federal requirements (NIH GPS, section 7.4*).*

For four sampled claims, we determined that WIV claimed indirect costs at a rate of 11 percent, or 3 percent greater than the allowable rate of 8 percent.

Travel Costs Did Not Meet Federal Requirements

We determined that $5,752 in travel costs paid with NIH grant funds were unallowable for the reasons listed below. Travel costs are allowable as a direct cost when providing a direct benefit to the grant-funded project. Consistent with the organization's established travel policy, these costs for employees working on a grant-supported project may include associated per diem or subsistence allowances and other travel-related expenses. If a recipient organization has no established travel policy, Federal Travel Regulations issued by GSA will be used to determine the amount that may be charged for travel costs. Those regulations include maximum per diem and subsistence rates. Alcohol is generally an unallowable expense (NIH GPS, section 7.9.1).

We determined that a payment totaling $3,285 for the transportation and accommodation costs of an EcoHealth employee attending a conference in October 2016 was unallowable. The employee was traveling under a non-NIH grant. Travel costs are required to provide direct benefit to the grant-funded project.[32] A coding mistake resulted in the charge to the NIH-funded grant, and EcoHealth concurred with our determination.

We determined that a payment totaling $2,128 for a meeting room and meal costs at a hotel on February 3, 2016, was unallowable. The support provided for the claim was an attestation of

[32] GPS Section 7.9.1.

expenses. Travel costs are required to be supported by source documentation and be adequately documented.[33] EcoHealth noted that the original receipt had been lost. EcoHealth officials documented the costs to the best of their knowledge. The attestation is not sufficient to support the claiming of costs to the grant.

We identified a claim for a one-night hotel stay on April 14, 2015, totaling $601, which was above the allowable per diem amount of $268. The hotel costs above the per diem rate totaled $334 and were unallowable. Also included on this invoice was a claim for an alcoholic beverage totaling $5 that was unallowable, for a total of $339 in unallowable costs. Travel costs must be made according to established per diem rates and for allowable purposes.[34]

According to the indirect rates EcoHealth used at the time each of these payments were made, we computed an additional $1,876 in unallowable indirect costs associated with the unallowable travel payments.

Other Costs Did Not Meet Federal Requirements

Visa Costs

We identified an invoice for which EcoHealth claimed reimbursement for expedited processing fees for an H-1B visa totaling $2,500. Visa costs are generally allowable as part of recruiting costs on an NIH grant as long as they are incurred to recruit a new employee and result in the institution having an employee/employer relationship with the individual.[35] Expedited processing fees are generally unallowable unless and until they become part of standard processing fees (NIH GPS, section 7.9.1).

EcoHealth believed that the expedited processing was required due to a backlog in visa processing. We express no opinion as to the necessity of expedited processing; however, the $2,500 portion of the invoice covering expedited processing charged to NIH grants, along with the $896 in associated indirect costs, are not allowable.

Invoice-Related Overpayments

EcoHealth claimed $2,078 in invoice-related overpayments. In general, NIH grant awards provide for reimbursement of actual, allowable costs incurred and are subject to Federal cost principles. A cost may be considered reasonable if the nature of the goods or services acquired or applied and the associated dollar amount reflect the action that a prudent person would have taken under the circumstances prevailing when the decision to incur the cost was made.

[33] 45 CFR § 75.302(b)(3) and 45 CFR § 75.403(g).

[34] GPS Section 7.9.1.

[35] Temporary worker visas are for persons who want to enter the United States for employment lasting a fixed period of time, and are not considered permanent or indefinite.

A cost is allocable to a cost objective—that is, a specific grant, function, department, or other component—if the goods or services involved are chargeable or assignable to that cost objective according to the relative benefits received or other equitable relationship (NIH GPS, section 7.2).

EcoHealth claimed $2,052 in unallowable costs associated with a subaward to WIV. The subrecipient submitted an invoice that contained a duplicate charge for in vitro studies, and the amount was added twice to arrive at the total invoiced amount. Separately, a consultant requested a payment of $15,000, but the detailed invoice only totaled $14,981, or $19 less than the actual payment. EcoHealth paid the consultant the full $15,000, resulting in a $19 overpayment from the detailed invoice, and $7 in associated indirect costs.

POTENTIAL UNREIMBURSED COSTS FOR A GRANT AWARD

As of May 2022, EcoHealth provided us with documentation to demonstrate that it had unreimbursed costs of approximately $74,500. EcoHealth claims that these costs were the result of adjustments to fringe benefits and indirect cost rates that occurred after the initial claims were submitted. We did not independently verify the accuracy of this computation; however, NIH should perform further analysis to determine whether EcoHealth had any incurred, unreimbursed costs for grant R01AI110964. The notices of termination and suspension to EcoHealth did not indicate which costs NIH would reimburse if the enforcement action were lifted and the award resumed.

NIH notified EcoHealth on April 24, 2020, that it elected to terminate the project Understanding the Risk of Bat Coronavirus Emergence, funded under grant R01AI110964, for convenience. Later, on July 8, 2020, NIH notified EcoHealth that it withdrew its termination of grant R01AI110964 and reinstated the grant. However, in the same letter NIH suspended all activities related to R01AI110964 until these concerns have been addressed to NIH's satisfaction, citing 45 CFR § 75.371, Remedies for Noncompliance, and several GPS citations.

GPAM (Part H, Chapter 4, Par. 21) requires that the notice of post-award suspension of award activities must clearly indicate which costs the HHS operating division will reimburse if the enforcement action is ultimately lifted and the award resumed. Additionally, NIH GPS (section 7.9.1) provides that NIH will allow full credit to a recipient for the Federal share of otherwise allowable costs if the obligations are properly incurred by the recipient before suspension or termination—and not in anticipation of suspension or termination—and, in the case of termination, are not cancellable. The Grants Management Officer may authorize other costs in, or subsequent to, the notice of termination or suspension.

CONCLUSION

Despite identifying potential risks associated with research being performed under the EcoHealth awards, NIH did not effectively monitor or take timely action to address EcoHealth's compliance with some research requirements. After the Federal governmentwide pause on

gain-of-function research was lifted, HHS and NIH implemented specific procedures to assess and monitor research reasonably anticipated to create, transfer, or use an ePPP. Given the inherent risks of this type of work, NIAID had a policy to err on the side of inclusion when considering whether to refer potential ePPP research to the NIAID DURC/P3CO Committee under the P3CO process. NIH determined that research under EcoHealth awards did not involve ePPP research, and as such, did not refer the proposed research to the HHS P3CO Committee for additional review. Nevertheless, NIH added a special term and condition in EcoHealth's awards requiring immediate notification if the research resulted in certain specified benchmarks involving log growth increases.

NIH provided limited guidance on how EcoHealth should comply with this specific requirement. EcoHealth never provided separate notice under that special term and condition because EcoHealth believed annual progress reports would constitute immediate notification. In addition, EcoHealth did not in a timely manner submit an annual progress report, nor did NIH in a timely manner follow up on the late report until nearly 2 years after its due date. Although NIH concluded the progress report identified virus growth that met certain benchmarks, EcoHealth's inability to obtain scientific documentation from WIV limited NIH's ability to assess EcoHealth's position that it had notified NIH/NIAID of meeting certain benchmarks in the Year 4 progress report and possibly conclude whether the research involved ePPP. As a result, NIH missed opportunities to more effectively monitor EcoHealth's research. With improved oversight, NIH may have been able to take more timely corrective actions to mitigate the inherent risks associated with this type of research.

Lapses in complying with NIH's monitoring procedures limited NIH and EcoHealth's ability to effectively monitor Federal grant awards and subawards to understand the nature of the research conducted, identify potential problem areas, and take necessary corrective action. Furthermore, these lapses limited NIH and EcoHealth's ability to determine how these grant funds were used, and mitigate the risk of noncompliance with Federal requirements and internal policies and procedures.

Our oversight work has continually demonstrated that grant-awarding agencies' oversight of subrecipients, whether domestic or foreign, is challenging. This is partly due to governmentwide regulations that NIH follows that are designed to have a prime grant recipient monitor the activities of a subrecipient, rather than requiring the grant-awarding agency—in this case NIH—to conduct active monitoring of subrecipients. For foreign subrecipients, the effectiveness of the prime recipient's monitoring may depend on the level of cooperation between the recipient and the subrecipient. In certain countries in which research is performed, there may be a risk that larger political or governmental issues may impede cooperation and prime recipients will have limited ability to effectively monitor their foreign subrecipients. Although documentation indicates that WIV cooperated with EcoHealth's monitoring for several years, WIV's lack of cooperation with the international community following the COVID-19 outbreak—consistent with the response from China—limited EcoHealth's ability to monitor its subrecipient, and greater transparency is needed about

information from WIV.[36] While the larger risks associated with political or governmental challenges may be hard to fully address under the grant process, NIH should assess how it can best mitigate these issues and ensure that it can oversee the use of NIH funds by foreign recipients and subrecipients.

We believe NIH has begun to take action to address some issues found in our audit. However, additional work is needed to ensure that NIH is able to fulfill its mission to enhance health, reduce illness and disability, and ensure grant funds are used for their intended purpose.

RECOMMENDATIONS

We recommend that the National Institutes of Health:[37]

1. ensure that EcoHealth accurately and in a timely manner reports award and subaward information, including in:

    a. recipient progress reports;

    b. the Federal Funding Accountability and Transparency Act of 2006, Subawarding Reporting System; and

    c. recipient-audited financial statements;

2. implement enhanced monitoring, documentation, and reporting requirements for recipients with foreign subrecipients;

3. define the process and timeline for what NIH considers "immediate notification" as it relates to specific award conditions intended to report unexpected research outcomes;

4. ensure that administrative actions such as terminations are performed in compliance with Federal regulations and HHS policies and procedures, and appropriate notifications of appeal rights are provided;

5. work with EcoHealth to recover identified unallowable costs, along with salary costs in excess of the NIH salary cap and bonus costs that were not sampled;

6. work with EcoHealth to determine whether EcoHealth had any unreimbursed costs at the time award R01AI110964 was terminated;

[36] As reported by the National Intelligence Council, China has likely impeded investigations related to the origins of COVID-19.

[37] The recommendations to NIH and EcoHealth are numbered to correspond with how each entity labeled the corresponding recommendation in its comments on the draft report.

7. assess whether NIAID staff are following the NIAID P3CO policy, including erring on the side of inclusion when determining whether proposed research should be referred to the NIAID DURC/P3CO Committee for research proposals that may involve ePPP;

8. based on information provided in this audit and any other information available to NIH, consider whether it is appropriate to refer WIV to HHS for debarment and exercise continued monitoring and enforcement activities as appropriate over the course of the grant awards and subawards; and

9. ensure for any future NIH grant awards that EcoHealth has addressed the deficiencies noted in the report.

We recommend that EcoHealth Alliance:

1. prepare subaward and consultant agreements that contain all required information and are accurate,

2. submit progress reports by the required due date,

3. comply with requirements to immediately notify NIH of conditions that materially impact the ability to meet award objectives,

4. ensure that it has the ability to access all records related to its research conducted at subrecipient locations,

5. properly identify subawards in financial statements, and

6. report subawards according to FFATA requirements.

We recommend EcoHealth Alliance refund to the Government $89,171 in unallowable costs consisting of:

1. salary costs claimed in excess of the NIH salary cap totaling $10,627,

2. bonus costs totaling $15,977,

3. indirect and fringe benefits associated with salary and bonus costs totaling $17,836,

4. Ph.D. education tuition costs totaling $13,951 and associated indirect costs of $4,641,

5. indirect costs totaling $13,037 claimed by a subrecipient,

6. travel costs totaling $5,752 and associated indirect costs of $1,876,

7. visa costs of $2,500 and associated indirect costs of $896,

8. subaward costs of $2,052, and

9. professional fees costs of $19 and associated indirect costs of $7.

NATIONAL INSTITUTES OF HEALTH AND ECOHEALTH COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

In written comments, NIH stated that it concurred or generally concurred with our recommendations and provided actions taken or planned to address them. EcoHealth stated it concurred with our first recommendation but did not directly state whether it concurred or did not concur with the remaining recommendations. EcoHealth identified two substantive areas of disagreement with the reported findings: (1) the timeliness of EcoHealth's Year 5 progress report and (2) whether an experiment exhibited "enhanced growth."

After reviewing the comments, we maintain that all of our findings and recommendations are valid. Below, we separately describe NIH's and EcoHealth's comments and provide OIG responses, as applicable.

NIH COMMENTS FOR RECOMMENDATIONS 1 THROUGH 9

Regarding recommendations 1, 4, and 8, NIH concurred and provided additional support on actions implementing the OIG recommendations. On August 19, 2022, NIH notified EcoHealth of specific award conditions to address accurate and timely reports of award and subaward information. These conditions included onsite subrecipient facility inspections every 6 months, withdrawal of automatic no-cost extensions and carryover authorities, and a requirement to submit semiannual progress reports. Furthermore, NIH stated that it will ensure that administrative actions are performed in compliance with Federal regulations.

Regarding recommendations 3, 5, 6, and 9, NIH concurred and noted actions that it will perform within 90 days of the publication of the report that will address the recommendations. The procedures include revising NIH policies to include a definition for the process and timeline for immediate notification as it related to unexpected research outcomes, working with EcoHealth to recover any identified unallowable costs, and determining whether EcoHealth had unreimbursed costs at the time the R01AI110964 award was terminated. Furthermore, NIH stated it will work with EcoHealth to ensure that the deficiencies noted in this report are being satisfactorily addressed.

Regarding recommendation 2, NIH generally concurred and stated that it will evaluate best practices across the Government for overseeing awards issued to domestic recipients that, in turn, oversee foreign subrecipients. Regarding recommendation 7, NIH concurred and has

established a working group to assess the current process for review and oversight of proposed research involving ePPPs.[38]

NIH also provided technical comments on our draft report, which we addressed as appropriate. NIH's comments, excluding technical comments, are included in their entirety as Appendix I.

OFFICE OF INSPECTOR GENERAL RESPONSE

We appreciate the cooperation NIH provided during the course of our audit and the proactive steps taken thus far to address our report findings and recommendations.

ECOHEALTH COMMENTS FOR RECOMMENDATIONS 1, 5, AND 6

Regarding recommendations 1, 5, and 6, EcoHealth noted that it had implemented procedures or taken actions to address the recommendations and related findings. EcoHealth stated that it has updated and revised its subaward and consultant agreements to contain required language and subaward identification, and has instituted measures to correct omissions on the agreements. EcoHealth further stated that it has instituted policies to ensure that it properly identifies subawards in its financial statements, and has provided all required FFATA reporting forms requested by NIH.

OFFICE OF INSPECTOR GENERAL RESPONSE

We appreciate the cooperation EcoHealth provided during the course of our audit and the proactive steps taken thus far to address our report findings and recommendations.

ECOHEALTH COMMENTS FOR RECOMMENDATION 2

Regarding recommendation 2, EcoHealth stated that it will continue to submit all required progress reports and indicated disagreement with the OIG finding that EcoHealth submitted its R01AI110964 Year 5 progress report late. EcoHealth stated that the Year 5 progress report was written and uploaded to the NIH online portal for submission by EcoHealth staff in July 2019, ahead of the September deadline. However, when EcoHealth staff attempted to submit the Year 5 report during late July 2019, the grant had been renewed for an additional 5 years, and the NIH system locked EcoHealth out from submitting the report. EcoHealth stated that NIH staff did not follow up with a request to EcoHealth for a Year 5 report, NIH did not answer EcoHealth's direct questions, and NIH did not return phone calls. EcoHealth noted the fact that because the new award was made, work was allowed to continue, and no requests for an official Year 5 report submission were made by NIH, which suggested to EcoHealth staff that they were in compliance with the submission requirement.

[38] NIH has established the working group of the National Science Advisory Board for Biosecurity, a Federal advisory committee that addresses issues related to biosecurity and dual-use research, at the request of the Government.

OFFICE OF INSPECTOR GENERAL RESPONSE

We acknowledge in our report that EcoHealth's Year 5 progress report was initiated on NIH's online portal in July 2019; however, we have no evidence that the progress report was fully uploaded to the online portal at that time. Furthermore, we have no evidence that there was any correspondence between EcoHealth and NIH describing technical difficulties with uploading the progress report on time. Ultimately, the progress report was not submitted until August 2021.

ECOHEALTH COMMENTS FOR RECOMMENDATION 3

Regarding recommendation 3, EcoHealth stated it will continue to comply with requirements to notify NIH of conditions that materially impact its ability to meet award objectives, and indicated disagreement with the OIG finding that it did not immediately notify NIH of conditions that materially impact its ability to meet award objectives. On the issue of timely reporting results to NIH, EcoHealth stated that: (1) the amended annual Notice of Award document did not use the phrase "immediately notify" and (2) NIH failed to provide a timeframe for notification in either the letter indicating that these experiments were approved or in the NIH Notice of Award. EcoHealth further stated that it did, in fact, notify NIH in a timely manner about these results by reporting the results of the experiment in an earlier progress report. In addition, EcoHealth stated that OIG made an incorrect statement in the report.

Specifically, EcoHealth stated OIG was incorrect in stating that NIH believed there was evidence that the research conducted by EcoHealth's subrecipient WIV during Year 5 resulted in "enhanced growth," thus triggering the special term and condition to immediately notify NIAID and potentially requiring the research undergo review under the HHS P3CO Framework. EcoHealth stated that the contention that it failed to report enhanced growth that would have required additional P3CO review as gain-of-function research was based on a misinterpretation of what the experiment in question actually showed. Specifically, EcoHealth indicated that it had reported on the same experiment in its Year 4 report submitted on time in 2018, and at that time EcoHealth had emailed a copy of its submitted Year 4 report to NIH and requested a timeslot to discuss the Year 4 report, the planned Year 5 work, and a renewal proposal.

OFFICE OF INSPECTOR GENERAL RESPONSE

The Notice of Award dated June 18, 2018, associated with the Year 5 funding, requires EcoHealth to notify NIAID grants officials immediately if certain benchmarks are met involving log growth increases and was what we used to determine whether EcoHealth's actions aligned with terms and conditions of the award. Furthermore, as we indicate in this report, our audit did not assess scientific results for any of the experiments or make any determination regarding the accuracy of NIH's or EcoHealth's interpretations of the Years 4 and 5 research results. Our audit found that NIH's own evaluation of the Year 5 progress report concluded that the research was of a type that should have been reported immediately to NIH. In an associated recommendation to NIH, we recommended NIH define the process and timeline for what NIH

considers "immediate notification." We agreed with NIH's assessment that reporting research in a progress report does not constitute immediate notification.

ECOHEALTH COMMENTS FOR RECOMMEDATION 4

Regarding recommendation 4, EcoHealth stated that, to the best of its ability, it will do all possible to ensure it can access and supply all records related to research conducted at subrecipient locations. However, it finds misleading the reported statement that it was unable to obtain scientific documentation from a subrecipient. EcoHealth notes a number of events that impacted its ability to access certain records, specifically that NIH instructed EcoHealth to cease the provision of funds to WIV 18 months before NIH requested EcoHealth obtain records from WIV, termination of the R01AI110964 grant, and significant geopolitical pressure and media coverage related to WIV, EcoHealth, and NIH-funded research.

OFFICE OF INSPECTOR GENERAL RESPONSE

OIG's report recognizes the impact that the COVID-19 outbreak had on EcoHealth's ability to receive cooperation from WIV. Furthermore, we recognize the general limitations associated with oversight of foreign subrecipients by prime recipients. However, EcoHealth is required by Federal regulations to ensure access to records from WIV. This record access requirement is important to ensure grantees are accountable for funds provided and that results of the research are available to NIH. The challenges EcoHealth experienced in getting records from WIV provides support for OIG's recommendation to NIH to enhance monitoring of foreign subrecipients so that NIH can take steps to mitigate the risks that non-cooperation by foreign Governments may pose to future awards and associated research.

ECOHEALTH COMMENTS FOR THE NINE MONETARY RECOMMENDATIONS

Regarding the nine monetary recommendations, EcoHealth stated that it reimbursed NIH for the total reported unallowable costs and provided NIH with details on the amounts of allowable but unreimbursed costs. However, EcoHealth disagreed with the OIG interpretation of Federal requirements for some items of cost and is seeking clarification from NIH. Specifically, EcoHealth stated that bonus costs are incentive payment allocations that may be deemed allowable under existing Federal guidelines, and that the bonuses and associated fringe benefit and indirect costs are allowable. EcoHealth disagreed with the questioning of Ph.D. education tuition costs, as the staff member is undergoing training in research methodology that is within the scope and type of research conducted through the NIH-funded project. EcoHealth disagreed with the questioned costs associated with one travel cost that was missing travel expense documentation but for which EcoHealth submitted corroborating documentation including price estimates, traveler information, and meeting agendas. EcoHealth disagreed with the questioned costs for visa costs and stated that the expense was justifiable given the need to rapidly engage an employee with a highly specialized skill set and background.

OFFICE OF INSPECTOR GENERAL RESPONSE

We maintain that all of our monetary recommendations are valid and in accordance with Federal regulations and the NIH Grants Policy Statement. Despite EcoHealth not fully agreeing with our interpretation of some of these requirements, EcoHealth stated that it did, in fact, repay the full amount of reported unallowable costs to NIH.[39] EcoHealth did not provide us with any new information or documentation that supported revising any reported unallowable costs. EcoHealth did request further clarification from NIH on certain costs, and we will review any guidance provided by NIH.

EcoHealth's comments are included in their entirety as Appendix J.

[39] As part of our audit recommendation followup process, we will request documentation that supports any repayment of funds to NIH for the unallowable costs we identified in this report.

APPENDIX A: AUDIT SCOPE AND METHODOLOGY

SCOPE

We obtained a list of all NIH grant and cooperative agreement awards to EcoHealth, and all subawards made by EcoHealth during the period FY 2014 through FY 2021. Our audit covered three NIH awards to EcoHealth totaling approximately $8.0 million, which included $1.8 million of EcoHealth's subawards to eight subrecipients. Appendix E includes a detailed list of EcoHealth's NIH awards and subawards.

We selected 150 transactions totaling $2,578,567 from EcoHealth's accounting system to determine whether the costs claimed were in compliance with Federal requirements. We used a nonstatistical methodology to select the transactions, which covered costs claimed under the three grants in our audit. We focused our selection on ensuring coverage of costs over our entire audit period, while including a variety of costs such as salaries, fringe benefits, subawards, professional fees, travel, supplies, telephone, publication, and indirect costs.

Of the 150 transactions we selected for review:

- 92 transactions were from grant number R01AI110964 totaling $1,525,012,
- 43 transactions were from grant number U01AI151797 totaling $751,949, and
- 15 transactions were from grant number U01AI153420 totaling $301,606.

We reviewed the transactions in accord with the cost principles in 45 CFR part 75 and with additional requirements located in the NIH GPS.

We determined that internal control was significant to our audit objectives. We assessed internal controls and compliance with laws and regulations necessary to satisfy the audit objectives, which included a review of NIH and EcoHealth's policies and procedures related to using, managing, and monitoring grant funds. However, because our review was limited to these aspects of internal control, it may not have disclosed all internal control deficiencies that may have existed at the time of this audit. Any internal control deficiencies we found are discussed in this report.

We conducted our fieldwork from June 2021 to August 2022, which included visiting EcoHealth's offices in New York City.

METHODOLOGY

To accomplish our first audit objective, we:

- interviewed NIH and NIAID officials familiar with the grant award and monitoring process;
- reviewed email communications and other correspondence between NIH and EcoHealth to gain insight on the types of interactions that occurred during the performance of the grant awards;
- reviewed Peer Review Summary Statements;
- reviewed required financial and programmatic reports;
- reviewed NIH oversight of EcoHealth's compliance with terms and conditions stated in the Notices of Award;
- reviewed NIH's oversight and reporting requirements associated with enhanced potential pandemic pathogens;
- as applicable, reviewed steps NIH took to ensure research was not anticipated to create, use, or transfer enhanced potential pandemic pathogens; and
- discussed the results of our audit with NIH.

To accomplish our second audit objective, we:

- interviewed EcoHealth officials familiar with the grant award and monitoring process,
- reviewed EcoHealth's policies and procedures,
- reviewed EcoHealth's subrecipient agreements,
- reviewed EcoHealth's subrecipient risk assessments,
- reviewed EcoHealth's subrecipient monitoring checklists,
- reviewed required financial and programmatic reports that EcoHealth submitted to NIH,
- selected and reviewed 150 transactions across the 3 NIH awards comprised of different types of transactions for allowability, and

- discussed the results of our audit with EcoHealth.

We conducted this performance audit in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

APPENDIX B: REQUIREMENTS ASSOCIATED WITH REVIEWING RESEARCH INVOLVING ENHANCED POTENTIAL PANDEMIC PATHOGENS

NIH describes potential pandemic pathogens as bacteria, viruses, and other microorganisms that are likely highly transmissible and capable of wide, uncontrollable spread in human populations as well as highly virulent, making them likely to cause significant morbidity and/or mortality in humans. On limited occasions, when NIH determines it is justified by compelling public health need and conducted in very high biosecurity laboratories, NIH has supported certain research that may be reasonably anticipated to create, transfer, or use potential pandemic pathogens resulting from the enhancement of a pathogen's transmissibility or virulence in humans. The Government and HHS define such research as ePPP research. NIH-supported ePPP research requires strict oversight and may only be conducted with appropriate biosafety and biosecurity measures.

The White House Office of Science and Technology Policy and HHS announced on October 17, 2014, that the Government was launching a deliberative process to assess the potential risks and benefits associated with a subset of life sciences research known as "gain-of-function" studies. During the period of deliberation, the Government instituted a pause on funding for any new studies that include certain gain-of-function experiments involving influenza, SARS, and MERS viruses. Specifically, the funding pause applied to gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. During this pause, the Government was not funding any new projects involving these experiments and encouraged those conducting this type of work—whether federally funded or not—to voluntarily pause their research while risks and benefits were reassessed. The funding pause did not apply to the characterization or testing of naturally occurring influenza, MERS, and SARS viruses unless there was a reasonable expectation that these tests would increase transmissibility and/or pathogenicity.

The HHS P3CO Framework was established in 2017. The HHS P3CO Framework describes measures responsive to and in accordance with the White House Office of Science and Technology Policy guidance to assess the potential risks and benefits associated with ePPPs. The Department's adoption of the HHS P3CO Framework satisfies the requirement for lifting the research funding pause on certain gain-of-function research. The HHS P3CO Framework is intended to guide HHS funding decisions on research that is reasonably anticipated to create, transfer, or use ePPPs.[40]

NIAID implemented the HHS P3CO Framework by developing a standard operating procedure *NIAID Extramural Potential Pandemic Pathogen Care and Oversight (P3CO).* This procedure

[40] The U.S. Government Accountability Office report *HHS Could Improve Oversight of Research Involving Enhanced Potential Pandemic Pathogens*, GAO-23-105455, January 2023, available at https://www.gao.gov/products/gao-23-105455, found unclear policy and other policy gaps that may allow proposed research involving altered pathogens with pandemic potential to occur without appropriate oversight.

indicates that NIAID's P3CO risk assessment process begins with a review by program staff of all applications, proposals, supplements, and progress reports being considered for funding that involve research with a PPP. When NIAID program staff review proposed research involving a PPP, they shall err on the side of inclusion and refer proposed research that may be subject to the HHS P3CO Framework to the NIAID DURC/P3CO Committee to determine whether the research is subject to the HHS P3CO Framework review process. See Table 4 for roles and responsibilities of funding agencies and HHS.

Table 4: Summary of Funding Agency and Department Responsibilities Under the HHS P3CO Framework

Entity	Responsibilities
Funding Agency	• Conduct standard scientific merit review • Refer proposed research that is reasonably anticipated to create, transfer, or use ePPPs to department-level review • Provide relevant information necessary to department-level review • Participate in department-level review process, as requested • Consider recommendations resulting from department-level review • Make funding decision, stipulating terms and conditions of award including additional risk mitigation measures, if appropriate • Report relevant information on funding decisions to HHS and the White House Office of Science and Technology Policy • Ensure implementation of and adherence to required risk mitigation procedures and other terms and/or conditions of award, if funded
HHS	• Convene multidisciplinary group to review proposed research determined by funding agency as being reasonably anticipated to create, transfer, or use ePPPs • Critically evaluate proposed research including risk-benefit assessment and proposed risk mitigation plan • Consider eight criteria for guiding HHS funding decisions and additional relevant factors and information • Develop recommendations on acceptability for HHS funding, including suggestions for additional risk mitigation measures and/or terms and conditions of award, if funded

APPENDIX C: PEER REVIEW OF ECOHEALTH APPLICATIONS

NIH performed scientific peer reviews of the three EcoHealth grant applications covered under our audit scope prior to making the awards. The R01AI110964 and U01AI153420 reviews were conducted by the Clinical Research and Field Studies of Infectious Diseases Study Section, Infectious Diseases and Microbiology Integrated Review Group. The U01AI151797 review was performed by the NIAID Special Emphasis Panel Emerging Infectious Diseases Research Centers. The applications were scored at acceptable levels for further discussion and award approval. The results of a peer review are provided in a document known as a summary statement. A summary statement provides an overall summary of a review, critiques by reviewers, priority scores, budget recommendations, and administrative notes.

The peer review summary statement for the R01AI110964 application noted that the proposed studies were to determine factors that increase the risk of zoonotic CoV emergence in people by studying CoV diversity in a critical zoonotic reservoir (bats) at sites of high risk for emergence (wildlife markets) in an emerging disease hotspot (China). The statement provided that, given the SARS outbreak in 2002 and the emergence of MERS, the research is significant as it relates to advancing knowledge of the zoonotic potential of coronaviruses.

The peer review summary statement for the U01AI151797 application noted that the study was focused on the identification of new, emerging viruses in Southeast Asia, which is a hotspot of viral activity with significant threat to human health. The approach was based on the identification of viral spillovers by means of studying the pathogen in wild animals and performing surveillance targeting high-risk communities.

The peer review summary statement for the U01AI153420 application noted that the study focused on the Nipah virus and aimed to understand why these virus outbreaks appear to only occur in the western part of Bangladesh despite the virus, its bat reservoir, and the primary route of transmission being present throughout the country. It explored human factors, virus temporal dynamics, and pathogenicity and transmissibility of diverse Nipah virus isolates.

APPENDIX D: PRE-AWARD AND AWARD PROCEDURES

NIH addresses potential risks posed by applicants during the pre-award and award process using a risk-based approach that considers factors such as an applicant's financial stability, quality of management systems, history of performance, whether an entity is foreign or domestic, reports and findings from audits, and ability to effectively implement statutory, regulatory, or other requirements imposed on non-Federal entities. Some of the key steps are outlined below.

- NIH uses the electronic Research Administration (eRA),[41] an automated system that maintains all of the checklists, worksheets, and progress reports generated to document the application and review process. In addition, for new or competing continuation grant awards made to a foreign organization or those with a foreign component,[42] NIH obtains the necessary clearances from the Department of State.[43]

- As part of the pre-award process, NIH uses two checklists maintained in eRA to assess grant applicant risk: the Grants Management checklist and the Program checklist. The Grants Management checklist covers topics that address administrative requirements to ensure completeness of an application, compliance with NIH and HHS policies, and compliance with other Federal regulations and requirements. The Program checklist is used to verify compliance with programmatic requirements before the issuance of a competing award and to evaluate the scientific merit of the research.

  When completing the Grants Management checklist, NIH reviews information about an applicant's eligibility, financial integrity, and past performance.[44] Some sources NIH uses include:

  - *GSA SAM*. GSA SAM is an electronic, web-based system that is used to identify parties that are excluded from receiving Federal contracts, certain subcontracts, and other types of Federal financial and nonfinancial assistance and benefits.

  - *The Federal Awardee Performance and Integrity Information System (FAPIIS)*. FAPIIS provides publicly available information about an institution's integrity, business ethics, and past performance after receiving a financial assistance award.

[41] The eRA is an online interface through which grant applicants, recipients, and Federal staff at NIH can access and share administration information related to research grants.

[42] A foreign component is defined as performance of any significant element or segment of the project outside the United States either by the recipient or by a researcher employed by a foreign organization, whether or not grant funds are expended (NIH GPS, section 16.2).

[43] NIH's Grants Narrative Process Cycle Memorandum, September 30, 2018.

[44] These risk factors are described at 45 CFR § 75.205.

- Once the preparation of an award is complete, eRA generates an Award Worksheet which summarizes the budget and results from the Grants Management and Program checklists. The checklists provide results of an applicant's risk to determine whether issuing awards to an organization is appropriate.

APPENDIX E: NIH GRANT AWARDS TO ECOHEALTH AND ECOHEALTH'S SUBAWARDS

Table 5: Funding Awarded to and Spent by EcoHealth*

Award Number	Award Title	Award Amount	Amount Spent
R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	$3,748,715	$3,376,503
U01AI153420	Study of Nipah virus dynamics and genetics in its bat reservoir and of human exposure to NiV across Bangladesh to understand patterns of human outbreaks	1,155,842	478,971
U01AI151797	Understanding Risk of Zoonotic Virus Emergence in EID Hotspots of Southeast Asia	3,052,312	1,529,259
Award and Expenditure Totals		**$7,956,869**	**$5,384,733**

* Grants awarded cover the audit period of FY 2014 to FY 2021. Grant expenditures are as of July 2021, the latest available records at the time the audit fieldwork began.

Table 6: List of NIH Awards to EcoHealth

Issue Date FY	Award Number	Award Title	Budget Year	Action Date	Action Amount
2014	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	1	5/27/2014	$666,442
2015	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	2	6/10/2015	630,445
2016	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	3	7/22/2016	611,090
2017	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	4	5/26/2017	597,112
2018	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	5	6/18/2018	581,646
2019	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	6	7/24/2019	733,750
2019	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	6	8/5/2019	(71,770)
2020	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	6	4/27/2020	(369,819)
2020	R01AI110964	Understanding the Risk of Bat Coronavirus Emergence	6	7/13/2020	369,819
				Subtotal	**$3,748,715**
2020	U01AI153420	Study of Nipah virus dynamics and genetics in its bat reservoir and of human exposure to NiV across Bangladesh to understand patterns of human outbreaks	1	9/15/2020	$580,858
2021	U01AI153420	Study of Nipah virus dynamics and genetics in its bat reservoir and of human exposure to NiV across Bangladesh to understand patterns of human outbreaks	2	7/1/2021	574,984
				Subtotal	**$1,155,842**
2020	U01AI151797	Understanding Risk of Zoonotic Virus Emergence in EID Hotspots of Southeast Asia	1	6/17/2020	$1,546,744
2020	U01AI151797	Understanding Risk of Zoonotic Virus Emergence in EID Hotspots of Southeast Asia	1	8/28/2020	0
2021	U01AI151797	Understanding Risk of Zoonotic Virus Emergence in EID Hotspots of Southeast Asia	2	6/11/2021	1,505,568
				Subtotal	**$3,052,312**
				Total Direct NIH Funding to EcoHealth	**$7,956,869**

Table 7: List of EcoHealth's NIH-Funded Subawards*

Subrecipient	Foreign/ Domestic	Funding Agency	Federal Award Number	Federal Award Project Period	Subaward Amount
Wuhan Institute of Virology	Foreign (China)	NIH/NIAID	R01AI110964	06/01/2014 - 05/31/2019	$598,611
Wuhan University School of Public Health	Foreign (China)	NIH/NIAID	R01AI110964	06/01/2014 - 05/31/2019	201,221
Institute of Epidemiology Disease Control and Research	Foreign (Bangladesh)	NIH/NIAID	U01AI153420	09/15/2020 - 06/30/2025	174,186
International Centre for Diarrhoeal Disease Research, Bangladesh	Foreign (Bangladesh)	NIH/NIAID	U01AI153420	09/15/2020 - 06/30/2025	61,853
Henry M. Jackson Foundation	Domestic (Bethesda, MD)	NIH/NIAID	U01AI151797	06/17/2020 - 05/31/2025	114,372
Conservation Medicine	Foreign (Malaysia)	NIH/NIAID	U01AI151797	06/17/2020 - 05/31/2025	241,807
WHO-CC for Research and Training on Viral Zoonoses, Chulalongkorn University	Foreign (Thailand)	NIH/NIAID	U01AI151797	06/17/2020 - 05/31/2025	215,945
The University of North Carolina at Chapel Hill	Domestic (Chapel Hill, NC)	NIH/NIAID	U01AI151797	06/17/2020 - 05/31/2025	194,375
				Total of EcoHealth's NIH-Funded Subawards	**$1,802,370**

* These subawards were in place during the audit period from FY 2014 through FY 2021 and represented the subawards for which EcoHealth had expenditures as of July 2021, the latest available accounting records from EcoHealth at the time the audit fieldwork began.

APPENDIX F: FEDERAL REQUIREMENTS FOR TERMINATING AND SUSPENDING GRANT AWARDS

According to HHS regulations (45 CFR § 75.372), a grant award may be terminated by the:

- HHS awarding agency if the non-Federal entity fails to comply with the terms and conditions of the award;

- HHS awarding agency for cause;

- HHS awarding agency with the consent of the non-Federal entity, in which case the two parties must agree upon the termination conditions including the effective date and, in the case of partial termination, the portion to be terminated; or

- non-Federal entity upon sending to the HHS awarding agency written notification setting forth the reasons for such termination, the effective date, and, in the case of partial termination, the portion to be terminated.

Furthermore, HHS regulations (45 CFR § 75.374) require HHS awarding agencies to provide a non-Federal entity an opportunity to object and provide information and documentation challenging the suspension or termination actions according to written process and procedures published by the HHS awarding agency. The HHS awarding agency must comply with any requirements for hearings, appeals, or other administrative proceedings to which the non-Federal entity is entitled under any statute or regulation.

NIH GPS Section 8.7 covers grant appeals procedures. It requires the formal notification of an adverse determination to contain a statement of the recipient's appeal rights and indicates that there be an NIH official specified in the notification. Furthermore, if the first level NIH review of an appeal is adverse to the recipient, or if a recipient's request for review is rejected, the recipient has an option to submit a request to the HHS Departmental Appeals Board for further review within 30 days after receiving the final NIH decision.

APPENDIX G: FEDERAL REQUIREMENTS FOR SUBRECIPIENT MONITORING

According to 45 CFR § 75.342, non-Federal entities are responsible for oversight of the operations of Federal award-supported activities. The non-Federal entity must monitor its activities under Federal awards to assure compliance with applicable Federal requirements and performance expectations are being achieved. Monitoring by the non-Federal entity must cover each program, function, or activity. Events may occur between the scheduled performance reporting dates that have significant impact upon the supported activity. In such cases, the non-Federal entity must inform the HHS awarding agency or pass-through entity as soon as the following types of conditions become known: problems, delays, or adverse conditions that will materially impair the ability to meet the objective of the Federal award. This disclosure must include a statement of the action taken, or contemplated, and any assistance needed to resolve the situation.

Pursuant to 45 CFR § 75.352(d), EcoHealth in its role as a pass-through entity must monitor the activities of a subrecipient as necessary to ensure: (1) the subaward is used for authorized purposes in compliance with Federal statutes, regulations, and the terms and conditions of the subaward; and (2) subaward performance goals are achieved. Pass-through entity monitoring of the subrecipient must include:

- reviewing financial and performance reports required by the pass-through entity;

- following up and ensuring that the subrecipient takes timely and appropriate action on all deficiencies pertaining to the Federal award provided to the subrecipient from the pass-through entity detected through audits, on-site reviews, and other means;

- issuing a management decision for audit findings pertaining to the Federal award provided to the subrecipient from the pass-through entity as required by 45 CFR § 75.521;

- depending upon the pass-through entity's assessment of risk posed by the subrecipient (as described in paragraph (b) of this section), using monitoring tools that may be useful for the pass-through entity to ensure proper accountability and compliance with program requirements and achievement of performance goals, including:

    - providing the subrecipient with training and technical assistance on program-related matters and

    - performing onsite reviews of the subrecipient's program operations; and

- considering whether the results of the subrecipient's audits, on-site reviews, or other monitoring indicate conditions that necessitate adjustments to the pass-through entity's own records; and

- considering taking enforcement action against noncompliant subrecipients as described in 45 CFR § 75.371 and in program regulations.

APPENDIX H: SUBRECIPIENT AGREEMENTS LACKED REQUIRED DATA ELEMENTS

Table 8: Required Data Element and Number of Instances of Noncompliance From Reviewing 11 Subrecipient Agreements Pursuant to 45 CFR § 75.352(a)(1)

Required Data Element	Number of Instances of Noncompliance
Subrecipient's Name	No Instances
Subrecipient's Unique Entity Identifier	No Instances
Federal Award Identification Number	11 Instances
Federal Award Date of Award to the Recipient by the HHS Awarding Agency	11 Instances
Subaward Period of Performance Start and End Dates	No Instances
Amount of Federal Funds Obligated by This Action by the Pass-Through Entity to the Subrecipient	No Instances
Total Amount of Federal Funds Obligated to the Subrecipient by the Pass-Through Entity Including the Current Obligation	11 Instances
Total Amount of the Federal Award Committed to the Subrecipient by the Pass-Through Entity	11 Instances
Federal Award Project Description as Required by FFATA	No Instances
Name of HHS Awarding Agency, Pass-Through Entity, and Contact Information for Awarding Official of the Pass-Through Entity	10 Instances
Code of Federal Domestic Assistance (CFDA) Number and Name; the Pass-Through Entity Must Identify the Dollar Amount Made Available Under Each Federal Award and the CFDA Number at the Time of Disbursement	10 Instances
Identification of Whether the Award Is Research and Development	11 Instances
Indirect Cost Rate for the Federal Award	4 Instances

APPENDIX I: NATIONAL INSTITUTES OF HEALTH COMMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

DATE: December 20, 2022

TO: Juliet T. Hodgkins
Principal Deputy Inspector General

FROM: Acting Principal Deputy Director, National Institutes of Health

SUBJECT: NIH Comments on Draft Report, "*The National Institutes of Health and EcoHealth Alliance Did Not Effectively Monitor Awards and Subawards, Resulting in Missed Opportunities to Oversee Research and Other Deficiencies*" (A-05-21-00025)

Attached are the National Institutes of Health's (NIH) comments on the draft Office of Inspector General's (OIG) report, "*The National Institutes of Health and EcoHealth Alliance Did Not Effectively Monitor Awards and Subawards, Resulting in Missed Opportunities to Oversee Research and Other Deficiencies*" (A-05-21-00025).

NIH appreciates the review conducted by OIG and the opportunity to provide the clarifications on this draft report. If you have questions or concerns, please contact Meredith Stein in the Office of Management Assessment at 301-402-8482.

/s/

Tara A. Schwetz, Ph.D.

Attachments

GENERAL COMMENTS OF THE NATIONAL INSTITUTES OF HEALTH (NIH) ON THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT ENTITLED: "THE NATIONAL INSTITUTES OF HEALTH AND ECOHEALTH ALLIANCE DID NOT EFFECTIVELY MONITOR AWARDS AND SUBAWARDS, RESULTING IN MISSED OPPORTUNITIES TO OVERSEE RESEARCH AND OTHER DEFICIENCIES" (A-05-21-00025)

The National Institutes of Health (NIH) appreciates the review conducted by the Office of Inspector General (OIG) and the opportunity to provide clarifications on this draft report. NIH respectfully submits the following general comments.

OIG Recommendation 1:
We recommend that the National Institutes of Health ensure that EcoHealth accurately and in a timely manner reports award and subaward information, including in:

- Recipient progress reports;
- The Federal Funding Accountability and Transparency Act of 2006, Subawarding Reporting System; and
- Recipient-audited financial statements

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation that NIH ensure that EcoHealth accurately and in a timely manner reports award and subaward information.

- In its August 19, 2022, letter to EcoHealth, NIH stipulated for R01AI110964 the following Specific Award Conditions, similar to Specific Award Conditions already implemented for other NIH grants awarded to EcoHealth.
    - EcoHealth must conduct or arrange for the conduct of onsite subrecipient facility inspections every 6 months to ensure that subaward activities are being properly executed.
    - EcoHealth must provide NIH with copies of updated subaward agreements for R01AI110964 that correct the deficiencies noted in the table above and demonstrate compliance with the NIH GPS 15.2.1 Written Agreement. The subaward agreements must state the correct F&A rate which, for foreign subrecipients is 8% (see NIH GPS 16.6).
    - The expanded authority for automatic no-cost extensions will be withdrawn. This will require that EcoHealth request and receive written prior approval from the National Institute of Allergy and Infectious Diseases (NIAID) before any extensions of the final budget period.
    - Automatic carryover authorities will be withdrawn. This will require EcoHealth to request and receive written approval to carry over any unobligated balances on all awards prior to carrying over unobligated balances from one budget period to any subsequent budget period.
    - EcoHealth is required to submit semi-annual RPPRs and Federal Financial Reports to NIAID.
    - EcoHealth will provide NIAID with copies of FSRS reporting for all subawards issued under the revised R01AI119064.

GENERAL COMMENTS OF THE NATIONAL INSTITUTES OF HEALTH (NIH) ON THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT ENTITLED: "THE NATIONAL INSTITUTES OF HEALTH AND ECOHEALTH ALLIANCE DID NOT EFFECTIVELY MONITOR AWARDS AND SUBAWARDS, RESULTING IN MISSED OPPORTUNITIES TO OVERSEE RESEARCH AND OTHER DEFICIENCIES" (A-05-21-00025)

- These specific award conditions will be in place for a period of at least 3 years from the date of the revised Notice of Award with an annual review to ensure proper compliance.

OIG Recommendation 2:
We recommend that the National Institutes of Health implement enhanced monitoring, documentation, and reporting requirements for recipients with foreign subrecipients.

NIH Response:
NIH generally concurs with OIG's finding and the corresponding recommendation.

NIH will evaluate how best to consider the OIG recommendation within the framework of 2 C.F.R. §§ 200.331 - 200.333, Subrecipient Monitoring and Management (Uniform Administrative Regulations). NIH will also need to consider 2 CFR 200.100(c), which states that "The Federal awarding agency may adjust requirements to a class of Federal awards or non-Federal entities when approved by the Office of Management and Budget…."

NIH will also evaluate best practices across government for overseeing awards issued to domestic recipients who in turn oversee foreign subrecipients. The results of this evaluation are anticipated to inform how NIH may implement the OIG recommendation.

OIG Recommendation 3:
We recommend that the National Institutes of Health define the process and timeline for what NIH considers "immediate notification" as it relates to specific award conditions intended to report unexpected research outcomes.

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation.

Within 90 days of the publication of this report, NIH will issue a Guide Notice and revise the NIH Grants Policy Statement to include a definition for the process and timeline for "immediate notification" as it relates to specific award conditions intended to report unexpected research outcomes.

OIG Recommendation 4:
We recommend that the National Institutes of Health ensure that administrative actions such as terminations are performed in compliance with Federal regulations and HHS policies and procedures, and appropriate notifications of appeal rights are provided.

GENERAL COMMENTS OF THE NATIONAL INSTITUTES OF HEALTH (NIH) ON THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) OFFICE OF INSPECTOR GENERAL (OIG) DRAFT REPORT ENTITLED: "THE NATIONAL INSTITUTES OF HEALTH AND ECOHEALTH ALLIANCE DID NOT EFFECTIVELY MONITOR AWARDS AND SUBAWARDS, RESULTING IN MISSED OPPORTUNITIES TO OVERSEE RESEARCH AND OTHER DEFICIENCIES" (A-05-21-00025)

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation.

NIH will ensure that administrative actions such as terminations are performed in compliance with Federal regulations and the Department of Health and Human Services (HHS) policies and procedures, and appropriate notifications of appeal rights are provided.

OIG Recommendation 5:
We recommend that the National Institutes of Health work with EcoHealth to recover identified unallowable costs, along with salary costs in excess of the NIH salary cap and bonus costs that were not sampled.

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation.

Within 90 days of the publication of this report, NIH will work with EcoHealth to recover identified unallowable costs, along with salary costs in excess of the NIH salary cap and bonus costs that were not sampled.

OIG Recommendation 6:
We recommend that the National Institutes of Health work with EcoHealth to determine whether EcoHealth had any unreimbursed costs at the time award R01AI110964 was terminated.

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation.

Within 90 days of the publication of this report, NIH will work with EcoHealth to determine whether EcoHealth had any unreimbursed costs at the time award R01AI110964 was terminated.

OIG Recommendation 7:
We recommend that the National Institutes of Health assess whether NIAID staff are following the NIAID P3CO policy, including erring on the side of inclusion when determining whether proposed research should be referred to the NIAID DURC/P3CO Committee for research proposals that may involve PPP.

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation.

The National Science Advisory Board for Biosecurity (NSABB) is currently charged with evaluating and providing recommendations to the Office of Science and Technology Policy (OSTP) and HHS on the effectiveness of the current oversight framework for research involving

enhanced potential pandemic pathogens (ePPPs). The NIH has established a Working Group of the NSABB to address this charge. As part of its evaluation, the NSABB will assess the current process adopted by HHS (including NIH and NIAID) for the review and oversight of proposed research involving ePPPs.

OIG Recommendation 8:
We recommend that the National Institutes of Health based on information provided in this audit and other information available to NIH, consider whether it is appropriate to refer WIV to HHS for debarment and exercise continued monitoring and enforcement activities as appropriate over the course of the grant awards and subawards.

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation.

NIH notes that debarment decisions are made by the HHS Suspension and Debarment Official, not NIH, and that any proposed debarments are subject to the Office of Management and Budget (OMB) guidelines to agencies on governmentwide debarment and suspension (nonprocurement) in 2 CFR 180.

OIG Recommendation 9:
We recommend that the National Institutes of Health ensure for any future NIH grant awards that EcoHealth has addressed the deficiencies noted in the report.

NIH Response:
NIH concurs with OIG's finding and corresponding recommendation.

In its August 19, 2022, letter to EcoHealth, NIH stated, "the NIH reserves the right to take additional compliance actions as needed, such as disallowing funds or imposing additional specific award conditions, if the HHS Office of Inspector General identifies other noncompliance and/or recommends such actions as a result of its audit of EcoHealth." Therefore, within 90 days of the publication of this report, NIH will work with EcoHealth to ensure that the deficiencies noted in this report are being satisfactorily addressed.

APPENDIX J: ECOHEALTH COMMENTS

22 December 2022

Sheri L. Fulcher
Regional Inspector General for Audit Services
Office of Audit Services, Region V
233 North Michigan, Suite 1360
Chicago, IL 60601

Re: Report Number. (A-05-21-00025)

Dear Ms. Fulcher,

Thank you for providing a draft of the report entitled *The National Institutes of Health and EcoHealth Alliance Did Not Effectively Monitor Awards and Subawards, Resulting in Missed Opportunities to Oversee Research and Other Deficiencies.* This letter represents an overview of our responses to the Findings and Recommendations. (Detailed comments, keyed to specific issues, are contained in the attached Appendix.)

This OIG audit report covers National Institute of Health (NIH) and EcoHealth Alliance (EHA) compliance with Federal requirements to ensure proper monitoring and use of grant funds for three NIH awards to EHA totaling approximately $8.0 million for the period covering FY2014 through FY2021. The OIG audit objectives were to determine whether: (1) NIH monitored grants to EHA in accordance with Federal requirements; and (2) whether EHA used and managed its NIH grant funds in accordance with Federal requirements. **EHA welcomes the OIG oversight and has collaborated fully and transparently with this audit.**

We note that the OIG did not find significant issues with EHA's grant oversight and compliance, summarizing its findings as follows: "EcoHealth had steps in place to conduct risk assessments of its subrecipients, and also had standardized checklists to document routine monitoring of its subrecipients." EHA accepts OIG's recommendations on how to ensure that subawards are compliant with Federal requirements; how to ensure compliance with subrecipient monitoring and reporting; and how to comply better with certain public disclosure requirements associated with reporting subaward funding. In fact, **EHA had already corrected certain procedures addressed by the OIG during the time period covered by the audit, or corrected them once we were notified of a finding by the OIG audit team.**

We note the additional DHHS OIG audit team finding that EHA "did not always use its grant funds in accordance with Federal requirements, resulting in $89,171 in unallowable costs." This

amounts to roughly 1% of the NIH grants awarded to EHA: put another way**, the OIG found that EHA did comply with Federal requirements 99% of the time**.

EHA has already reimbursed the NIH for the total in unallowable costs as determined by the OIG. We found the OIG analysis instructive in several cases where EHA did not follow the appropriate requirement (in two cases these involved expenses as small as a $19 overpayment and a miscoded $5 beverage) and have corrected these minor errors. In other cases, EHA disagrees with the OIG interpretation of the Federal requirements and we are seeking clarification on these instances with the NIH.

During the audit process, we discovered that EHA has been underpaid by the NIH for indirect cost allocation equivalent to $126,391. The OIG notes this in the report and EHA has pursued reimbursement of these funds owed to EHA by the NIH.

There were only two substantive areas of disagreement with the OIG over their findings – one concerning the timeliness of EHA's progress Year 5 Progress report on a R01 grant from NIAID, the other an issue around whether an experiment that showed unexpected levels of genome copies at an early stage constituted "enhanced growth" that required further review. We do not agree with the OIG's characterization of these two issues, for reasons outlined in detail in the Appendix.

During the 8-year period covered by this OIG audit, the Federal requirements changed multiple times, and EHA policies changed to match them. Many of the findings occurred under a different management team. Additionally, the OIG audit does not reflect a series of new requirements placed on EHA contracts by NIH that have already been put in place and set standards that are above and beyond the normal procedures for subrecipients.

The audit process has helped EHA to sharpen its policies and practices to enable even better compliance with NIH and other Federal rules in the future. We appreciate the professionalism of the OIG review staff and the analysis provided in your report.

Sincerely,

Peter Daszak, PhD
President, EcoHealth Alliance
520 Eighth Avenue, Suite 1200
New York, NY 10018, USA
www.ecohealthalliance.org

APPENDIX:
EcoHealth Alliance responses to DHHS OIG audit report recommendations*

A. We recommend that EcoHealth Alliance:

1. *prepare subaward and consultant agreements that contain all required information and are accurate,*

EcoHealth Alliance Response: We agree with this recommendation and have already instituted measures to correct omissions on contracts and agreements. Many of the instances identified by DHHS OIG were from over 5 years ago and were copy-paste errors resulting from inadvertent reuse of a prior contract template. EcoHealth Alliance has updated and revised all its subaward and consultant agreements to contain required language and subaward identification.

2. *submit progress reports by the required due date,*

EcoHealth Alliance Response: EcoHealth Alliance will continue to submit all required annual, semi-annual, or other progress reports by the deadlines set by NIH, to the best of our ability. The DHHS OIG report suggests that EcoHealth Alliance submitted its R01-AI110964 Year 5 progress report late, and that the report indicates 'enhanced growth' of a recombinant virus in an approved experiment. We refute this statement: it does not provide a full review of the facts. We have provided extensive documentation to NIH and to the DHHS OIG to support this point (see below).

Regarding the timely submission of our report: **EcoHealth Alliance's Year 5 progress report was written and uploaded into the NIH online portal for submission by EcoHealth Alliance staff in July 2019 -- ahead of the September deadline.** When EcoHealth Alliance staff attempted officially to submit the report during late July 2019, the grant had been renewed (24 July 2019) for an additional 5 years and the NIH system locked EcoHealth Alliance out from submitting a Year 5 report. NIH staff did not follow up with a request to EcoHealth Alliance for a Year 5 report, despite frequent communication among EcoHealth Alliance staff and NIH program and grants management staff during that time. Direct questions from EcoHealth Alliance staff remained unanswered by NIH, and phone calls were not returned. The fact that the new award was made, work was allowed to continue, and no requests for an official Year 5 report submission were made by NIH, suggested to EcoHealth Alliance staff that we were in compliance. The next communication on this issue from NIH was on 23 July 2021, approximately two years later, requesting submission of the Year 5 report. EcoHealth rapidly complied and submitted its Year 5 report within 11 days, but only after considerable intervention from NIH staff to circumvent its system's lockout. Even though the grant was terminated and

* Text in italics in this Appendix is quoted verbatim from the DHHS OIG Draft Report Findings and Recommendations.

then suspended, and no funding was available to work on the progress reports, EcoHealth Alliance continued to comply with NIH reporting requests and has submitted a Year 6 and Year 7 report on this grant.

Regarding the allegation that the report indicated 'enhanced growth' of a recombinant virus:

3. *comply with requirements to immediately notify NIH of conditions that materially impact the ability to meet award objectives,*

EcoHealth Alliance Response: To the best of its ability, EcoHealth Alliance will continue to comply with requirements to notify NIH of conditions that materially impact its ability to meet award objectives, and to do this in a timely manner, and as directed. However, we refute the suggestion that EcoHealth Alliance failed to comply with the timeliness of reporting or of conditions that materially affect the award objectives.

Firstly, on the issue of the timing of our reporting the results of coronavirus experiments to NIH: As we have already indicated to the DHHS OIG with documentary evidence in support, and in previous letters to NIH, NIH did not use the phrase 'immediately notify' in the document of record for the amended annual award – the Notice of Award. Additionally, NIH failed to provide a timeframe for notification in either the letter indicating that these experiments were approved, or in the NIH Notice of Award. Finally, we did, in fact, notify NIH in a timely manner about these results, having provided this information rapidly after being sent it by the laboratory that conducted the experiments in China.

Secondly, on the issue of the material nature of the experimental findings in the report: DHHS OIG states that "*according to NIH's evaluation of EcoHealth's progress report for Year 5 of the grant, NIH believed there was evidence that the research conducted by EcoHealth's subrecipient WIV during Year 5 resulted in enhanced growth by more than one log, thus triggering the special term and condition to immediately notify NIAID and potentially requiring the research to undergo review under the HHS P3CO Framework.*" **This statement is not factually correct and EcoHealth Alliance has provided both a detailed explanation and documentation to both the NIH and the DHHS OIG to support EcoHealth Alliance's statement. The contention that EcoHealth Alliance failed to report "enhanced growth" that would have required additional P3CO review as "gain of function" research is based on a misinterpretation of what the experiment in question actually showed.**

Specifically, EcoHealth Alliance reported on the same experiment in its Year 4 report submitted on time in 2018 and at that time (25 April 2018) EcoHealth Alliance emailed a copy of its submitted Year 4 report to NIH and requested a timeslot to discuss the Year 4 report, the planned Year 5 work, and a renewal proposal. This call happened on 18 July 2018. **At no time then or until well after this grant was terminated in April 2020, was there any comment from NIH re. experimental results or the timing of reporting**. Additionally, as indicated in our letter to NIH October 26th 2021, and in our extensive responses to the DHHS OIG's earlier drafts of this report, in virological terms, "virus growth" normally refers to viral titer measuring the concentration of infectious viruses by plaque assay. The experiment we reported to NIH actually shows genome copies per gram, not viral titers. We have been advised by senior virologists that data on genome copies per gram usually do not accurately equate to viral titer, since genomic

material from inactivated, incompletely formed, or dead virus are also measured. Viral titers were not measured in the experiments detailed in the Year 4 or 5 reports. We also note that the genome copy data for recombinant viruses are only enhanced relative to the WIV1 backbone at the earliest part of the experiment and by the endpoint, there was no discernably significant difference among the different viral types, suggesting that these differences, if real, were transient. Given the small number of mice used, it is also uncertain whether the survival and weight loss data were statistically relevant, and as no further replications of this experiment were performed, we are unable to corroborate these initial results. We assume that these were the rationale NIH used at the time for not highlighting this work as requiring further clarification or secondary review under the "gain of function" guidelines.

4. *ensure that it has the ability to access all records related to its research conducted at subrecipient locations,*

EcoHealth Alliance Response: To the best of its ability, EcoHealth Alliance will continue to do all possible to ensure that it can access and supply all records related to its research conducted at subrecipient locations. However, EcoHealth Alliance finds the DHHS OIG report statement misleading in suggesting that EcoHealth Alliance was simply "*unable to obtain scientific documentation from a subrecipient*". It is correct that on 5 November 2021 NIH wrote to EcoHealth Alliance requesting scientific documentation from its subrecipient, the Wuhan Institute of Virology (WIV). These included lab notebooks and the original data used to produce graphs for the year 4 and 5 reports to NIH. However, DHHS OIG omitted the following critical information: 1) 18 months prior to this request (on 19 April 2020) NIH instructed EcoHealth Alliance "to cease providing any funds from the above noted grant to the WIV", and that EcoHealth Alliance responded on 21st April 2020 to confirm that no funds had been sent to WIV under the award, nor had any contract been signed, and that EcoHealth Alliance would comply with all NIH's requirements; 2) NIH terminated the award on 24th April 2020 "for convenience"; 3) during 2020 and 2021, the WIV, EcoHealth Alliance, and the research that NIH funded became subject to significant geopolitical pressure and almost daily misreporting in the media globally, including repeated unsubstantiated allegations that lab notebooks had been hidden, or forged, or data corrupted, and these acts covered up. During that time, EcoHealth Alliance was subjected to political attacks in the USA and abroad, including efforts to remove our eligibility for federal funding based on disinformation and hearsay.

NIH's request for documentation 18 months after a project was de-funded, terminated and then suspended, and the intense media and political pressure are extraordinary circumstances that should be noted in the report. These conditions and particularly the political tensions between the Chinese and US governments at the time effectively shut down communications among scientists at the WIV (a Chinese government laboratory) and EcoHealth Alliance staff, making it impossible for EcoHealth Alliance to secure the requested data. Despite this, and as DHHS OIG notes, EcoHealth Alliance made reasonable attempts to comply with NIH's requests, including supplying further unpublished data. EcoHealth Alliance also forwarded the request to WIV staff, but has not yet received a response.

EcoHealth Alliance always has and continues routinely to share its unpublished data from its research with its NIH program officers through regular progress reports. Genetic

sequences relevant to EcoHealth Alliance's work are routinely deposited in the NIH GenBank so that they can be used by other scientists globally. Indeed, even after NIH terminated EcoHealth Alliance's award, EcoHealth Alliance continued to file annual reports with NIH to provide unpublished data. In addition, EcoHealth Alliance submitted analyses of the NIH-supported work for publication in leading international peer-reviewed journals so that the data and results are available publicly.

5. *properly identify subawards in financial statements, and*

EcoHealth Alliance Response: Prior to 2019, our CPA consultant advised EcoHealth Alliance not to list foreign subawards in financial statements. We have provided documentation to DHHS OIG to confirm that this was the professional advice we received. Notwithstanding this advice, for the past 3-years, EcoHealth Alliance has provided full subaward identification in all internal and public financial statements and has instituted policies to ensure this will continue to be our practice.

6. *disclose subawards according to FFATA requirements.*

EcoHealth Alliance Response: EcoHealth Alliance has provided all required FFATA reporting forms since NIH first requested these documents. Copies of FFATA reporting for all subawards have been provided to NIH upon request and at NIH's current direction continue to be provided to NIH 30 days following EcoHealth Alliance's submissions to the FFATA system.

B. We recommend EcoHealth Alliance refund to the Government $89,171 in unallowable costs consisting of:

EcoHealth Alliance Response: EcoHealth Alliance has already refunded this amount to NIH in full. However, we note that during our review of financial records as part of this audit, we identified $126,391 in allowable costs on three NIH awards that have not yet been reimbursed to EcoHealth Alliance. At NIH's request, on 16 December 2022, EcoHealth Alliance provided details of these unreimbursed costs, which we expect to recover in due course.

Despite our repayment of the $89,171 in costs that DHHS OIG has claimed are unallowable, EcoHealth Alliance maintains our previously-stated opinion that some of these expenditures are 'allowable' and others are reasonably disputed. We have provided rationale for this in the detailed responses below:

1. *salary costs claimed in excess of the NIH salary cap totaling $10,627,*

EcoHealth Alliance Response: EcoHealth Alliance has reimbursed this amount to NIH and agrees with DHHS OIG's finding here. EcoHealth Alliance made minor miscalculations in the time allotment of allowable salaries over the NIH GPS 4.2.10 Salary Cap/Salary Limitation. To address this EcoHealth Alliance employed a new time management system and software that

accurately captures and segregates all salary charges for NIH funded personnel that exceed Salary Cap/Salary Limitations.

2. *bonus costs totaling $15,977,*

EcoHealth Alliance Response: EcoHealth Alliance has reimbursed this amount to NIH. Nonetheless, EcoHealth Alliance disagrees with the DHHS OIG interpretation of *NIH GPS 7.9.1 Allowability of Costs/Activities*, which clearly allows bonus and incentive payments to be reimbursed by NIH. EcoHealth Alliance maintains that its policy of providing such payments to staff is: 1) based on performance and therefore referred to as providing "incentive payments"; 2) based on an "established plan" clearly indicated in the EcoHealth Alliance Employee Handbook; 3) established as an EcoHealth Alliance Board-approved operating procedure for more than 12 years; and 4) something that staff are made fully aware of *prior to* their performance (i.e. 'services rendered'). EcoHealth Alliance has received legal counsel corroborating its understanding that EcoHealth Alliance staff incentive payment allocations may be deemed "allowable" under existing Federal guidelines, and are in accord with standard criteria for interpreting and applying a statute or regulation.

3. *indirect and fringe benefits associated with salary and bonus costs totaling $17,836,*

EcoHealth Alliance Response: EcoHealth Alliance has reimbursed NIH for this expense. Nonetheless, EcoHealth Alliance disputes the portion of indirect and fringe corresponding to DHHS OIG's determination about the allowability of incentive payments to EcoHealth Alliance staff.

4. *Ph.D. education tuition costs totaling $13,951 and associated indirect costs of $4,641,*

EcoHealth Alliance Response: EcoHealth Alliance has reimbursed NIH for this expense. Nonetheless, EcoHealth Alliance disagrees with the DHHS OIG understanding of NIH GPS 7.9.1 Allowability of Costs/Activities that tuition payments are an unallowable cost. This staff member and graduate student is undergoing training in research methodology as part of a doctoral program that is precisely the scope and type of research and work conducted on the respective NIH funded project. EcoHealth Alliance believes this is an allowable cost because: 1) the staff member is conducting activities necessary to the Federal award; 2) the expense was incurred in accordance with established EcoHealth Alliance policies; 3) the tuition payments are reasonable and fair; 4) the employee is not 'attending Kingston University', since the graduate program is a part-time 'external candidate' PhD program with no required courses and all by research and thesis.

5. *indirect costs totaling $13,037 claimed by a subrecipient,*

EcoHealth Alliance Response: EcoHealth Alliance has reimbursed NIH for this expense. This was a simple error regarding the *de minimis* overhead rate for a foreign subrecipient on a contract dating back to 2015. US Federal agencies apply different *de minimis* rates and this

error was the result of using a single contract template based on an agency that allows a 10% rate on foreign subrecipients, versus the 8% allowed by NIH.

6. *travel costs totaling $5,752 and associated indirect costs of $1,876,*

EcoHealth Alliance Response: EcoHealth Alliance has reimbursed these costs to NIH. Two of these were simple miscoding errors. However, one travel cost in the amount of $2,808.43 is a valid allowable cost. At the time of travel (2016), the printed receipt for this approved, budgeted foreign travel expense was lost. EcoHealth Alliance now has a back-up system for receipt storage or capture and a policy for rapid follow-up with vendors to secure missing receipts, however that was not our policy at the time. When DHHS OIG requested this receipt in 2021, EcoHealth Alliance contacted the non-USA-based vendor, but this over-4-year-old expense was no longer on file with the vendor. We submitted corroborating documentation to DHHS OIG, including verified price estimates, the number of travelers/participants, and meeting-agendas. However, DHHS OIG did not consider these sufficient.

7. *visa costs of $2,500 and associated indirect costs of $896,*

EcoHealth Alliance Response: EcoHealth Alliance has reimbursed NIH for this expense. Nonetheless, EcoHealth Alliance disputes this finding. Expedited H1-B visa processing times take 15 business days. Regular H1-B processing times take between 3-to-6 months. At the time of this expenditure, due to the COVID-19 pandemic, regular processing times were further delayed. EcoHealth Alliance considered expedited visa expense justifiable given the need to rapidly engage an employee with a highly specialized skill set and background to work on a pandemic-delayed project during lock-down at the end of 2020.

8. *subaward costs of $2,052, and*

EcoHealth Alliance Response: EcoHealth Alliance agrees with this finding. This was a miscalculation on the part of EcoHealth Alliance's subaward in 2015 and was an error not noted at the time by the subaward or EcoHealth Alliance personnel. Since that time, we have instituted redundancy and cross checks in subaward receipts and processing and a commercial receipt storage and capture system that will reduce the opportunity for similar mistakes.

9. *professional fees costs of $19 and associated indirect costs of $7.*

EcoHealth Alliance Response: EcoHealth Alliance agrees with this finding. This was a copy-paste error on the part of program personnel. We have since instituted an internal third review of all payment requests submitted to our finance team to reduce the opportunity for similar mistakes.

Center for Health Security

Discussion on the Future Science and Technology of Biological Attribution

Summary of 6 December 2022 meeting organized by the Office of Science and Technology Policy

January 24, 2023

Johns Hopkins Bloomberg School of Public Health
Center for Health Security

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The views expressed in this publication and/or made by meeting attendees do not necessarily reflect the official policies of the US government, nor does mention of trade names, commercial practices, or organizations imply endorsement by the US government.

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Contents

Introduction

After a biological incident—whether it is natural, deliberate, accidental, or undetermined—there is an imperative to investigate and identify the cause of the incident, and attribute who, if anyone, is responsible. The ability to attribute responsibility for a biological incident (bioattribution) helps to ensure that the deliberate use of biological weapons may be fully prosecuted and those responsible are held accountable. Bioattribution capabilities may also serve as a deterrent for use of biological weapons. Such a capability is the result of an attribution investigation that integrates multiple data sources, including information collected by law enforcement and public health officials, intelligence information, and technical information about the biological agent and other biological and environmental samples collected. The process is complicated; it relies on technical methodology and social systems (ie, the ability to get samples and to have a trusted process) to produce the technical information and sampling for attribution. It is important to routinely evaluate the state of the science available for bioattribution to ensure that investigations may leverage state-of-the-art technology and that efforts are being made to overcome technical challenges.

Summary

On 6 December 2022, the Office of Science and Technology Policy (OSTP) hosted an unclassified, not-for-attribution roundtable discussion on the future of science and technology of biological attribution, including ~15 technical experts and US government (USG) stakeholders. The purpose of the daylong meeting was to provide OSTP and other USG stakeholders an opportunity to obtain information and viewpoints from individual subject matter experts from industry, academia, and national laboratories on the technical aspects—largely, laboratory analysis—of bioattribution. The technical experts came from a diverse range of backgrounds covering genomics, proteomics, bioanalytical chemistry, immunology, bioinformatics, virology, and synthetic biology. Discussions in the morning session focused on the current state of bioattribution technical capabilities with an emphasis on laboratory analysis of biological samples and ideal operating scenarios, and the afternoon discussion focused on pragmatic steps for the bioattribution field in the future. Early on, there was a discussion focused on whether an effort to exhaustively sequence all biological agents of interest to create a reference database was feasible and/or worthwhile. It was recognized that such an effort to exhaustively sequence everything of interest was not practical and that the future of technical bioattribution would need to operate without such a resource.

Significant discussion was dedicated to sample analysis techniques and identifying mid-term (5-10 years) technology development goals. Sample analysis methods generate significant amounts of data and rely on even greater amounts of public data.

Considering how that data is generated, processed, stored, shared, and represented was a common theme throughout the meeting, as it is the underpinning of bioattribution. The Genetic Engineering Attribution Challenge was discussed as an example of how public competitions could be used to make rapid advancements in the field as well as a case study for understanding data needs for building machine learning models for effective bioattribution. Machine learning methods are likely to gain prevalence and popularity in coming years, and it was discussed that the selection of a machine learning model will need to consider the intended use of the output information. Given the accepted lack of an exhaustive reference database, there was discussion on how to maximize the value of multiple pieces of data that each provide some unique insight. Lastly, experts thought that the role of the USG in bioattribution science and technology should be clarified and expanded—it was thought that the government could play a catalytic role in advancing bioattribution technology.

Dedicated research and development efforts are needed to overcome technical challenges in bioattribution, and it was noted that current incentive structures do not support developing a workforce to pursue careers in bioattribution. The technical experts agreed that continued conversation is needed and that the field needs to have more advancement as a community, and the experts expressed enthusiasm in continuing to work together. There was a positive sense in the room in support of future meetings, roundtable discussions, conferences, and community challenges to strengthen bioattribution capabilities.

Meeting Themes

The following themes were present in discussion throughout the day:

Methods: Laboratory analysis of biological samples was categorized into 3 fields of study: genomics, proteomics, and metabolomics. Analysis methods from these fields of study are needed to characterize complex mixtures/samples that may or may not contain living organisms. Capabilities within the field of genomics generally exceed those of proteomics and proteomics capabilities far exceed those of metabolomics. As opposed to PCR-based methods, today's genomic methods focus on sequencing the whole genome. A shortfall of current proteomic methods is the throughput, owing to the time required to run the analysis and the time required to reconfigure and prepare instrumentation between samples. It was noted that multiple independent measures providing the same result would be particularly helpful for attribution, and the ability to identify connectedness among samples from separate events would be valuable in identifying networks of individuals with malintent. Validated methods and core technologies in the public domain would provide an additional element of trust in the results.

Reference samples, databases, and big data: Much of the work surrounding bioattribution relies on matching the analytical output of an unknown sample to a previously collected reference sample or information in an existing database. However, it will not be possible to a priori categorize all of biology to create a database expansive enough to adequately address all future needs. There was discussion about making this problem tractable by investing in understanding smaller, representative subsets of different genera of organisms, for example, to develop a general understanding the genus. Some large databases do exist within industry but are the proprietary information of the companies that own them and should not be considered an available resource to others. It was noted that criminal prosecution relies on publicly available data.

There was general agreement that researchers should endeavor to publish any collected data in a reproducible and transparent manner. In addition to the data itself, there is a desire to include metadata in a standardized fashion. The conversation did not progress to the specificity of exactly what data and metadata would be most valuable in this context. However, some data repositories are growing unsustainably fast and are on pace to become less useful in the coming 2–5 years. Such efforts could be supported by the National Institute of Standards and Technology (NIST) and the National Center for Biotechnology Information (NCBI), and it was suggested that representatives from NIST and NCBI be included in future attribution conversations. There was discussion about cloud-based solutions in academia and industry, but, due to security practices, these solutions may not be feasible for all USG stakeholders. Dual use concerns surrounding what data is collected and aggregated, and how that information could be misused, will also need to be considered.

Genetic Engineering Attribution: One of the more notable activities in the field of bioattribution in recent years is the Genetic Engineering Attribution Challenge that occurred in 2020.[1] This public competition was intended to build upon an earlier academic publication in which the authors demonstrate an ability to predict the lab-of-origin of an engineered DNA plasmid.[2] Prize money was awarded to teams with the highest accuracy in predicting the lab-of-origin. This challenge served as a case study that was referenced during discussion throughout the day. This challenge used data from the nonprofit organization AddGene. The characteristics of the dataset that made it well suited for the challenge were 1) its size, 2) its public availability, 3) its standardized metadata, and 4) the distribution of entries across many academic laboratories. Competitors produced machine learning models that were marked improvements from the earlier publication. There are practical limitations to this work as the concept of operations relies on a bad actor having published their work, deposited their information in a public database, like AddGene, or someone having a priori knowledge of that actor's prior genetic engineering history. Additionally, this work is predicting who designed a sequence and not necessarily who made the sequence.

"Black box" machine learning methods: There are differences between technical and policy experts in their expectations for bioattribution data.[3] Some users of bioattribution data need and expect a rationale for why a machine learning algorithm produced a specific result, something that remains an inherent challenge of using deep learning based methods. One interesting finding from the Genetic Engineering Attribution Challenge was that neural networks perform well on attribution but that traditional machine learning methods also perform well. This suggests that there may not be a meaningful tradeoff in accuracy and explainability, and that technology development should proceed with the needs of the end users in mind. The use of deep learning methods may still provide value in pointing investigators in the right direction but likely would be insufficient as a standalone method of bioattribution. While noted as important, there was limited discussion as to the ideal level of human involvement in the operation of the machine learning algorithms.

Partial solutions: While there was a sense that a perfect solution will remain elusive, there was discussion on how helpful information can be generated from a sample. Such information includes if the pathogen had characteristics of being grown in a laboratory setting, if it underwent directed evolution, if the evolutionary chronometry aligns with what would be expected in nature, if there are abnormalities in the epidemiological data, and sometimes the function of the organism (or molecule). To support these goals, there was a desire to better understand how much variability exists in nature (ie, a baseline) and how much of the knowledge space is unknown. Although none of these processes will individually and conclusively link a biological weapons attack to the responsible party, the collective set of information may be able to.

Role of government: There does not appear to be a single office within the USG that "owns" the challenge of bioattribution. Having a dedicated responsible USG entity would be beneficial to technology research and development. There was a similar roundtable discussion held by the UK government several weeks prior to the USG meeting and intergovernmental collaboration would be beneficial. There are limited incentives for industry and academia, particularly early career scientists, to operate in this space; government can play a role to catalyze careers in bioattribution.

Moving Forward

This roundtable discussion will be the start of continued discussion and engagement. Moving forward, USG, industry, and academia all have roles to play:

Technological development: One clear gap identified was the throughput of proteomics assays. With such shortcomings being known and success metrics easily defined, the USG should invest in a program to develop technologies to more rapidly or cost

effectively generate data required for investigations. Additionally, there was some discussion about exploring federated learning, a method that would allow one entity to use another entity's data to train a machine learning model without exchanging the data, to overcome expressed concerns about disclosing propriety data. Work has been started in this space[4] and additional conversations among the technology developers (bioinformatics and cryptographic experts) and government and industry stakeholders would be required to determine if this is a viable path toward a generalizable and acceptable means for the USG to leverage industry-owned data in support of bioattribution.

Partial solutions: Given the acceptance that an exhaustive reference database will not be available, focus should be on how to maximize the contributions of information that answers questions tangential to identifying a specific individual or entity responsible for a biological event. These methods should be developed with the intent on integrating them into a generalized workflow and efforts should simultaneously be made on maximizing the value of the integration. The USG should consider funding such efforts in industry and academia.

Standardization: Future conversation will need to become more specific with regards to what data is collected, how it is processed, annotated, stored, and shared. This work could be coordinated through NIST or NCBI.

Conferences: The American Society for Microbiology (ASM) has previously hosted ASM Biothreats, an annual scientific conference dedicated to emerging research in the field of biothreats. The 2023 meeting could include a session on bioattribution to inspire broader audience engagement.

Community challenges: The Genetic Engineering Attribution Challenge demonstrated the ability to engage with individuals outside of the biology community and to make technical progress on defined problems in exchange for the possibility of winning a relatively small monetary prize. Future challenges could be developed and conducted to be more realistic of bioattribution activities by including less-than-perfect data sources. Additionally, such a challenge could require participants to curate and publicize data resources for future bioattribution work.

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