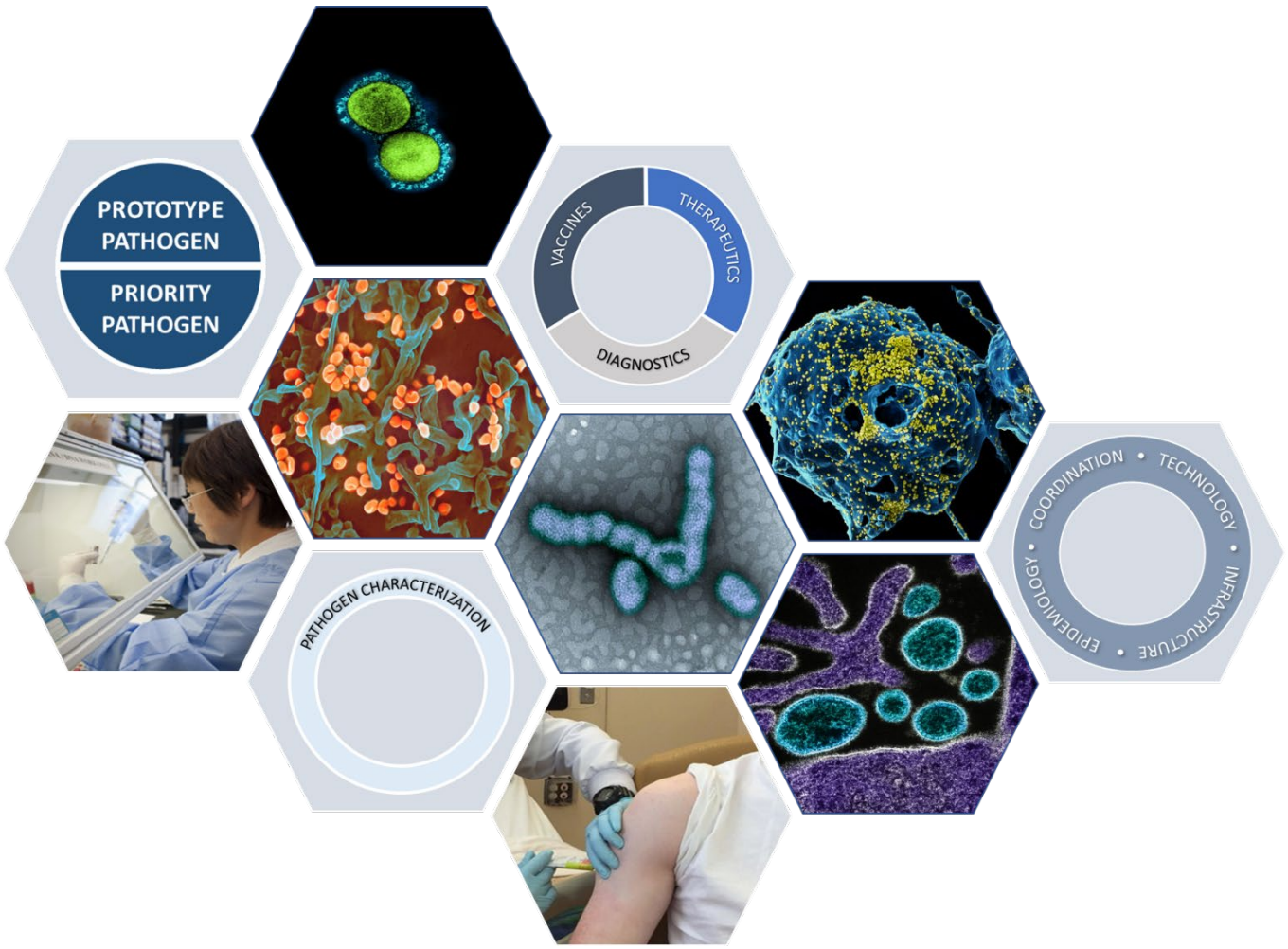
National Institute of Allergy and Infectious Diseases



NIAID PANDEMIC PREPAREDNESS PLAN

December 2021

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Background

The National Institute of Allergy and Infectious Diseases (NIAID) is committed to safeguarding the health of Americans and people around the world by conducting and supporting basic and applied research to better understand, treat, and ultimately prevent infectious diseases. NIAID developed this Pandemic Preparedness Plan, which leverages its broad research portfolio, long-standing expertise in product development, capacity to engage both domestic and international partners, and flexible infrastructure to support its mission to respond rapidly to emerging and re-emerging infectious disease threats.

The NIAID pandemic preparedness plan focuses predominantly on viruses that could cause epidemics or pandemics and prioritizes research on prototype-pathogens, representative pathogens from viral families known to infect humans, and high-priority pathogens most likely to threaten human health. Research and development will encompass preclinical research, translational, and early phase clinical studies to evaluate candidate medical countermeasures, such as vaccines, therapeutics, and monoclonal antibodies. Underpinning research and development preparedness efforts are novel epidemiology and surveillance programs, expanded pre-clinical and clinical infrastructure capacity, and a robust and coordinated communication structure. The NIAID Pandemic Preparedness Plan aims to ensure all intramural and extramural NIAID pandemic preparedness efforts are harmonized, and that collaboration will occur across the US Government (USG) and with foreign governments, industry, and international organizations.

Stakeholder engagement is a valuable part of the NIAID preparedness planning efforts. In November 2021, NIAID hosted a workshop that introduced the NIAID pandemic preparedness strategy and facilitated discussions with the scientific community on prioritizing prototype pathogens within viral groups of concern. Moving forward, NIAID will continue to engage the outside scientific community and federal partners to ensure preparedness planning efforts are collaborative, integrative, and aligned with current scientific research.

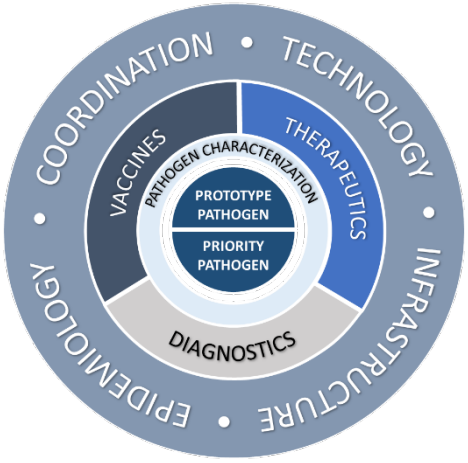
Introduction

The emergence and re-emergence of infectious diseases continues to threaten the health of Americans and people worldwide. In the past two decades NIAID has mounted major research responses and developed effective countermeasures to emerging infectious diseases including those caused by SARS-CoV-1, the 2009 H1N1 influenza virus, Middle East Respiratory Syndrome coronavirus (MERS-CoV), Ebola virus, Zika virus, and most recently SARS-CoV-2. The ongoing 2020 global pandemic caused by SARS-CoV-2 further has underscored the continual threat of newly emerging and re-emerging pathogens and the critical value of research in pandemic preparedness efforts. To prepare for future public health emergencies caused by infectious diseases, NIAID has developed a Pandemic Preparedness Plan that leverages its broad research portfolio, long-standing expertise in product development, capacity to engage both domestic and international partners, and flexible infrastructure. While it is recognized that pathogens other than viruses could lead to public health emergencies, the NIAID Pandemic Preparedness Plan focuses on viruses that could cause epidemics or pandemics.

Pathogens of concern, for the purposes of the NIAID Pandemic Preparedness Plan, are viruses that have the potential to cause a human epidemic or pandemic.

The goals for the NIAID Pandemic Preparedness Plan are to:

- Systematically **characterize pathogens of concern** and increase research and surveillance to identify threats before they emerge
- **Shorten timelines** between pathogen emergence or outbreak onset and authorization/approval of candidate diagnostics and medical countermeasures, such as therapeutics and vaccines
- **Bridge or eliminate existing gaps** in research, infrastructure, and technology and expand pre-clinical and clinical testing capacity



The NIAID Pandemic Preparedness Plan goals build on a foundation of pathogen-specific research that include advancing research on priority pathogens known to or having the potential for emerging as public health threats. Continuing to build a robust basic research portfolio and advancing translational science on these pathogens is essential for biomedical preparedness. In addition to known threats, effective preparedness must also account for unexpected emerging disease threats, commonly referred to as Pathogen(s) X. To mitigate risks associated with these yet unknown pathogens, NIAID will prioritize preparedness research on prototype-pathogens, which are select pathogens identified from viral families known to infect humans. Viruses are taxonomically organized into families based upon shared functional and structural similarities. Because of this, candidate vaccines developed against a prototype pathogen from a family may similarly work against other members in the same family. Through targeted basic and applied research on these prototype pathogens from each viral family of concern, the accrual of a solid foundation of knowledge and medical countermeasures (MCMs), such as therapeutics, vaccines, and monoclonal antibodies (mAbs), will

enable a rapid response when a Pathogen X emerges from any of the viral families of concern. This anticipatory approach will exponentially increase the preparedness and response portfolio and enable rapid movement of candidate MCMs into clinical trials.

NIAID will support the research, development, and testing of critical MCMs through Phase I/IIa clinical trials where appropriate, in coordination with other entities undertaking similar research worldwide. NIAID also will continue to provide the USG public health infrastructure with a robust pipeline of preparedness resources to shorten the response timeline when human viral disease threats emerge. NIAID, the lead NIH Institute for infectious disease research and MCM discovery, has broad capacity in infectious diseases and immunology and a history of preparing for and responding to domestic and global infectious disease threats. A central NIAID team will facilitate, coordinate, and harmonize preparedness research and development within the Institute. It also will communicate and coordinate with the NIH and other relevant USG agencies as well as appropriate entities outside the U.S., including key international organizations and foreign research partners.

To prevent widespread morbidity and mortality, the early detection of an emerging pathogen threat is essential. Therefore, in partnership with the CDC, USAID and other USG entities concerned with emerging infectious diseases, strategic epidemiological field studies undertaken by NIAID-supported centers and networks will provide key reagents and insights into viruses that have the potential to cause a human epidemic or pandemic. In addition, these efforts will be coordinated with similar global efforts already underway or planned so that informed worldwide surveillance and epidemiology is assured.

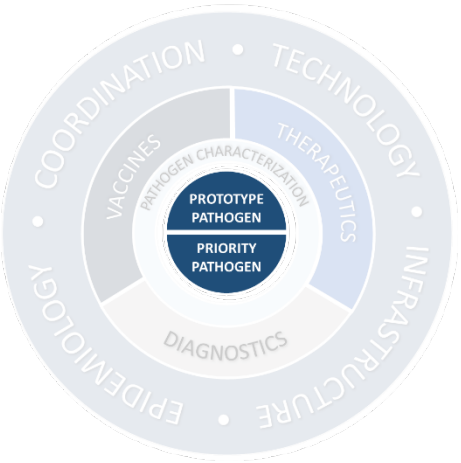
Technological advancements, such as platform technologies for MCMs, will also be crucial to the preparedness effort. The most promising platform technologies will need to be leveraged for development of vaccines, therapeutics, and diagnostics. Their products will also need to be evaluated clinically through an experienced and nimble clinical trial infrastructure that complies with rigorous regulatory standards. Developing and leveraging these cross-cutting elements across the preparedness research pipeline will enable NIAID to support the USG research effort that will underpin an effective response to public health emergencies caused by emerging or re-emerging infectious disease threats.

Preparedness-Response Continuum

Pandemic preparedness and response exist along a continuum, and it is important to operationally distinguish between the capacities associated with each. The extent of preparedness will determine the speed and effectiveness of a response. The NIAID preparedness research efforts will provide the reagents, roadmaps for product development and evaluation, scientific infrastructure, and study capacity needed for a robust research response to a future pandemic.

Conceptual Approach

Preparedness for major infectious disease outbreaks will save lives; rapid deployment of effective diagnostics, vaccines, and treatments can contain an outbreak before it expands into a larger epidemic or pandemic. Obtaining in-depth knowledge and developing MCMs for prototype pathogens within viral families that pose the highest risk for epidemics/pandemics is an effective strategy to prepare for future disease outbreaks. This approach was successfully applied during the global COVID-19 pandemic of 2020 when prior knowledge gained through the study of SARS-CoV-1 and MERS-CoV was leveraged to rapidly design vaccines, diagnostics, and therapeutics against SARS-CoV-2.



Priority and Prototype Pathogen Research

There are multiple virus families for which there are no available licensed vaccines, and many member viruses within families that have potential to cause significant human disease. Since it is not feasible to fully characterize the ~120 viruses known to cause human disease and develop MCMs for each, selection of representative viruses from each family offers a viable pathway to gain knowledge that may be applicable to part or all of a particular virus family. These representative viruses are considered **prototype pathogens.** For example, within the *Arenaviridae* family, Lassa, Junin, or other viruses could be selected as a prototypic pathogen(s). The ideal arenavirus prototype pathogen(s) would not only be a virus with a risk of causing an outbreak, but most importantly, would be one that shares functional and structural properties with viruses across the *Arenaviridae* family. Thus, increasing fundamental knowledge and developing MCMs for the prototype virus(es) not only provides ready potential solutions for these viruses, but also the framework for a rapid research and product development response to other viruses within that family should an outbreak occur. A schematic for how prototype pathogens are selected, studied, and brought to clinical trials is shown in Figure 1.

In addition to the prototype pathogen approach, NIAID will also characterize, develop reagents, and conduct pre-clinical and clinical testing of other pathogens that may not serve as prototypes, but that nonetheless threaten human health and thus are considered a high priority to study. We refer to these as **priority pathogens**. This pathogen-specific research prioritizes viruses most likely to cause significant human morbidity and mortality. While priority pathogens can also be prototype pathogens (e.g., Ebola virus), these two designations do not necessarily overlap. For instance, Zika virus of the Flaviviridae family is known to cause human morbidity, but it does not serve as a good prototype for development of MCMs for other Flaviviridae family members. Thus, NIAID will continue to support Zika virus research in the capacity of a priority pathogen. To ensure adequate coverage of viruses that pose a known threat to human health and Pathogen(s) X, NIAID will support both priority and prototype pathogen research through its pandemic preparedness strategy.

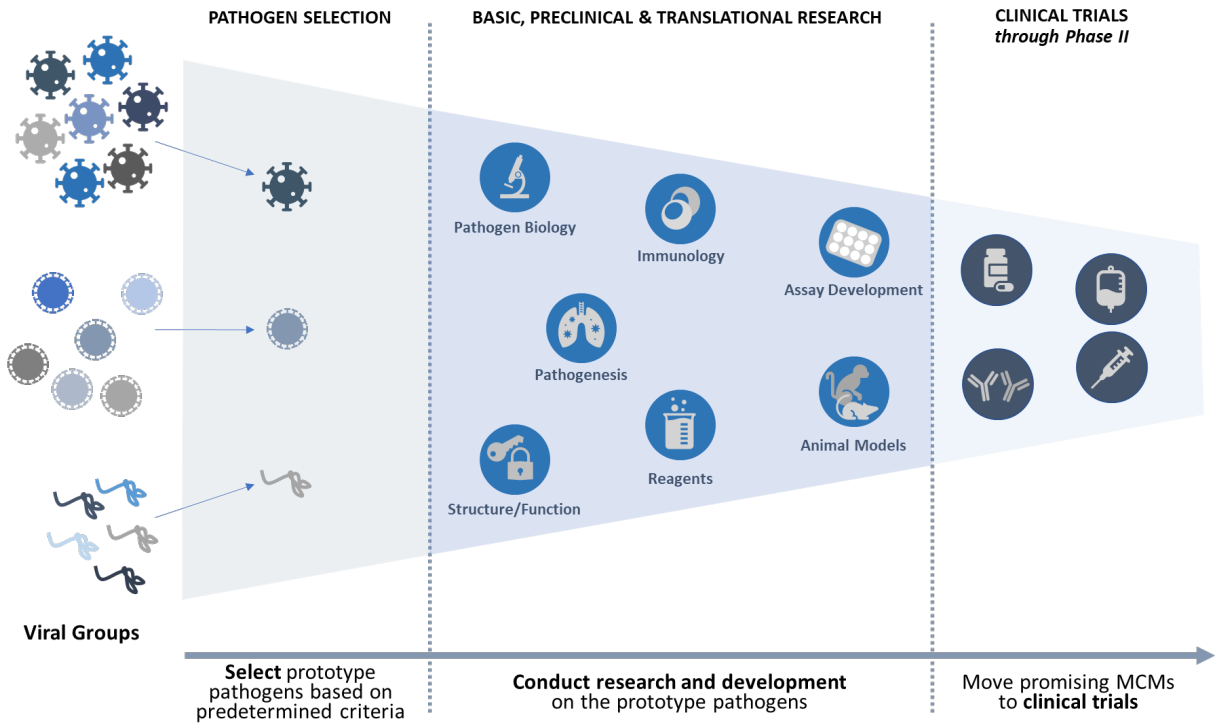
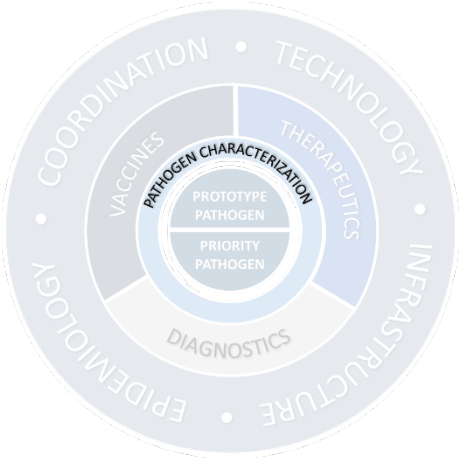


*Figure 1: **Prototype Pathogen Research and Development Process**. Schematic depicts the process by which prototype pathogens will be selected for additional study, preclinical and translational research activities, and clinical trials of promising MCMs.*

Preparedness Research and Development

The Pandemic Preparedness Plan will support critical studies to characterize prototype and priority pathogens, including understanding viral biology and structure, host immune responses, mechanisms of immune evasion, disease pathogenesis, and studies to develop assays and animal models of disease. Research and development will encompass preclinical and translational activities and will include expanded conduct of early phase clinical studies to evaluate candidate countermeasure safety and immunogenicity, or drug profile characteristics. Clinical trials of promising MCMs will include equitable representation of participants from traditionally underrepresented groups, all genders, and individuals across the lifespan.



Preclinical Research

Pathogen Biology, Pathogenesis, and Host Immunity

Developing products that can protect against pathogens of concern is an integrated process that requires basic and applied research. Fundamental knowledge of pathogen biology; structural properties; mechanisms of transmission, including identification of viral vectors; viral lifecycle; viral entry mechanisms and host receptors; tissue tropism; and host immune responses is critical to efforts informing the development of MCMs against new, emerging, or remerging pathogens.

Structure-Function Studies

Understanding the function of essential viral proteins will be necessary to enable structure-guided vaccine design, identify viral targets for the development of effective therapeutic candidates, and develop diagnostic and immunological assays. To facilitate this critical area of research, NIAID will support technologies including x-ray crystallography, nuclear magnetic resonance imaging, cryogenic electron microscopy, and high-throughput technologies, including computational modeling to characterize viral structural components.

Animal Models

Developing animal models that recapitulate human disease is a vital step toward understanding disease pathogenesis and mechanisms of immune protection as well as the assessment of MCM efficacy. Small animal models will be prioritized to enable rapid, scalable studies particularly valuable for screening countermeasure candidates for immunogenicity, drug candidate pharmacokinetics/pharmacodynamics, vaccine and therapeutic efficacy and safety. In parallel, development and characterization of large animal models, including non-human primates that closely recapitulate human disease, is pivotal to advance promising candidates toward clinical evaluation. NIAID will support the development of essential small and large animal models to better understand viral biology and to assist in vaccine and therapeutic development. NIAID also will ensure that well characterized animal models that recapitulate human disease are made available to the scientific community for evaluating priority MCMs.

Immunology and Assay Development

NIAID will support the design and development of serological assays that can serve as useful tools to evaluate MCMs, including evaluating the immunogenicity of promising vaccines and effectiveness of therapeutic candidates. These assays can also identify correlates of protection, identify antigen-specific responses to pathogens, and characterize cross-reactive responses to pathogens.

The design and development of approaches and research tools to assess and enhance cellular and tissue-specific immunity to specific pathogens and pathogen families will also be supported.

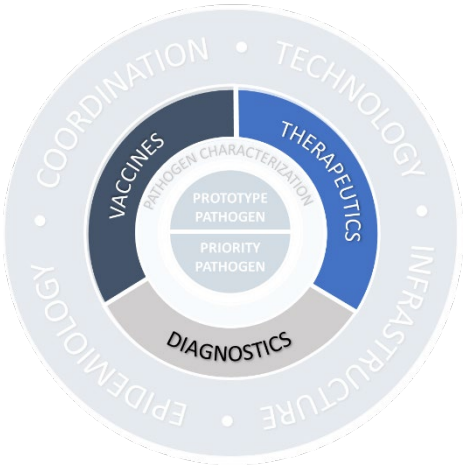
NIAID will provide for the expansion of specialized technologies related to high-throughput cell sorting/cytometry, immunologic assays, and sequencing, and expand support of genetic examination of zoonotic reservoirs that might contribute to emerging infectious diseases of global health importance.

Reagents and Resources

NIAID will support and coordinate the development and sharing of reagents and resources to accelerate fundamental research and the development of vaccines, therapeutics, immunological assays, and diagnostics. Reagent and resource development will include well characterized viral stocks, convalescent serum, and PBMCs to develop assays, protein or nucleic acid standards, mAbs, and animal models. The reagents will be put in NIAID-supported repositories and made available to the scientific research community.

Translational and Clinical Research

Diagnostics



NIAID will leverage its expertise in infectious diseases, genomics, proteomics, bioinformatics, and access to clinical samples to develop rapid-response diagnostics for biological threats and emerging infectious diseases. In close collaboration with other NIH institutes and USG agencies, NIAID will support the development new and improved point-of-care and home-based tests as well as ultrahigh-throughput central reference laboratory testing that can accurately detect signatures of infectious pathogens that are of high public-health consequence. NIAID will develop readiness strategies in collaboration with other USG agencies to ensure immediate authorized deployment of the necessary diagnostic testing as a frontline medical countermeasure following acknowledgement of an imminent public-health threat.

Therapeutics

NIAID will continue to support basic, translational, and clinical research efforts to identify promising targets for intervention and generate novel therapeutics that are both pathogen-specific and have broad-spectrum activity. Leveraging earlier successful partnerships (as for HIV drug development) and continuing the collaborative interactions that were established in response to the COVID-19 pandemic, NIAID will engage pharmaceutical companies to share libraries, medicinal chemistry, and drug development expertise to accelerate internal efforts to ensure the most promising drug candidates progress rapidly into clinical use.

Small Molecule/Antivirals

The Pandemic Preparedness Plan will respond to the pressing need for safe and effective therapeutics by building sustainable platforms for targeted drug discovery through the development of small molecules and antivirals that may be useful against a wide range or class of pathogens of concern. NIAID will evaluate and advance new drug candidates to the stage of being late Phase 2-ready. One existing program through which NIAID will develop safe and effective antivirals is the Antiviral Program for Pandemics (APP). The APP will focus on antivirals that directly act against viral targets, specifically for RNA viruses. Antivirals of interest will have broad use in the outpatient setting, reducing viral burden in the early stages of infection.

As part of the APP, NIAID will establish Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern. The centers will initially focus on novel, oral antivirals for SARS-CoV-2 and other coronaviruses and will expand to other pathogens of pandemic concern in future years.

These Centers will use the tools of structural biology, biochemistry, and systems biology to select essential virus-specific functions for targeting. Further, this platform will provide a means for identifying the conserved structures and functions shared between pathogens of concern that can be targeted for drug development.

Monoclonal Antibodies

Recent advances in mAb technologies have provided scientists with valuable tools to prevent and treat infectious disease. Innovation efforts in the selection and manufacture of mAbs reduced the time needed for their development. Their applicability in either prevention or treatment approaches make mAbs a powerful intervention against infectious disease, particularly essential in the case of an outbreak (as during the Ebola outbreak in central Africa and the COVID-19 pandemic). NIAID will support the development and characterization of panels of mAbs against prototype and priority pathogens. The mAbs that are identified as highly neutralizing or with broadly neutralizing capacity will be further characterized and developed into candidates for effective therapeutics and/or prevention approaches.

Broad-spectrum protection via immunomodulation, trained immunity, and related approaches

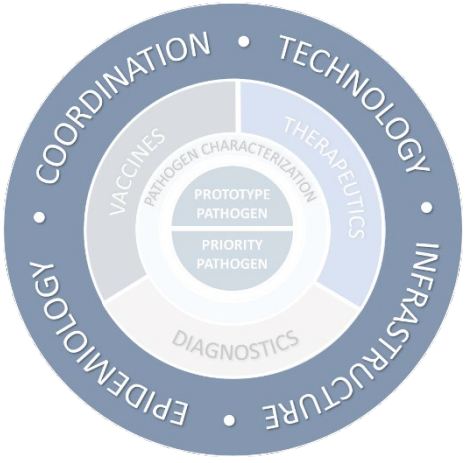
Recent advances in understanding host innate immunity highlight the potential value of non-antigen-specific protection as a bridge during development of antivirals and vaccines. NIAID will support the development and clinical evaluation of short-term, but broadly protective strategies including the use of inhaled or systemic immunomodulators. Research on vaccine-elicited, off-target protection has identified a molecular process termed *trained innate immunity*, by which certain live-attenuated or well-adjuvanted vaccines trigger long-lived epigenetic programs that enhance functions of innate immune cells, including monocytes and macrophages. NIAID will support basic and clinical research with the long-range objective of providing protection from severe disease early in a pandemic (prior to the availability of pathogen specific vaccines) through trained innate immunity.

Vaccines

Successful vaccine design and development can significantly alter the course of a pandemic. To address the need for safe and highly effective vaccines against new and emerging pathogens, NIAID will support work to define the key antigenic targets through the use of the prototype and priority pathogen approaches, solve structures of surface proteins, characterize the immunological response (including epitope mapping), support structure guided vaccine design, identify and characterize novel adjuvants that boost immunity and increase the breadth of immune responses while decreasing vaccine reactogenicity, and identify cellular receptors and tropisms. In addition, comprehensive reagents leading to the development of antigen-specific and serological assays would also provide the necessary tools for vaccine development.

Cross-cutting Preparedness Efforts

The ability of NIAID to prepare for and mount a rapid and effective research response to an emerging pathogen relies on knowledgeable staff, up-to-date facilities and flexible infrastructure, cutting-edge technology, and a robust, centralized coordination hub.



A dedicated preparedness coordination team of NIAID staff and scientists working closely with the NIAID Office of the Director will serve as the coordination hub for the NIAID pandemic preparedness efforts. This team will track the prototype pathogen research portfolio, ensuring adequate pathogen coverage and resource allocation to address scientific gaps. NIAID will continuously engage with leadership in other federal

agencies and international funders with preparedness and response capabilities to inform them on preparedness research progress.

The NIAID Pandemic Preparedness Plan outlines the cross-cutting epidemiology, infrastructure, technology, and coordination and communication approaches necessary to successfully prepare for future pandemics.

Epidemiology and Pathogen Discovery

Underpinning preparedness research and development is a robust global disease discovery and epidemiology program aimed at identifying emerging infectious disease threats, which are crucial for risk assessment, reagent collection, pandemic preparedness efforts and rapid response measures. Early discovery and appraisal of pathogens of concern is a major element of overall pandemic preparedness. Epidemiology and surveillance will ensure that we are able to rapidly identify, characterize, and act upon newly emerging and re-emerging pathogens in zoonotic reservoirs and in geographic regions where outbreaks are likely to occur. The NIAID PREMISE program (Pandemic Response Repository through Microbial and Immune Surveillance and Epidemiology) will contribute significantly to the pathogen discovery mission and overall pandemic preparedness. PREMISE will pair virologic and immunologic surveillance of viruses and facilitate the development of diagnostic tests and MCMs in anticipation of potential pandemic threats. To further pandemic preparedness, NIAID will utilize its global network of research centers to study how and when viruses and other pathogens emerge from wildlife and spillover into humans. The Centers for Research in Emerging Infectious Diseases (CREID) will enable early warnings of emerging diseases, facilitating a rapid response and potentially curbing potential disease threats before they develop into widespread pandemics. In addition, the NIAID Centers of Excellence for Influenza Research and Response (CEIRR) program will focus on the study of influenza in humans and at the human-animal interface and provide international research infrastructure needed to address zoonotic influenza outbreaks in humans or a pandemic.

NIAID will also liaise with other USG agencies and global partners to help support the enhancement of in-country capacity to expand worldwide surveillance, genetic sequencing, epidemiology, virus or viral variant discovery. Such coordination will help prioritize development of diagnostics, reagents, and MCMs.

Technology

NIAID will continue to support and advance platform technologies that can be leveraged to develop MCMs. By investing in research to develop specific MCMs for known threats and utilizing platform-based and prototype-pathogen approaches to allow for adaptation when unexpected outbreaks arise, NIAID and its partners–both domestic and international–can prepare to effectively combat future disease outbreaks. Broad, wide-range platforms that can be used to significantly reduce the time and cost required to bring MCMs to market. For example, mRNA and adenovirus vaccine platform technologies were successfully utilized during the COVID-19 pandemic to develop effective vaccines against SARS-CoV-2; these and other innovative technologies can be leveraged in the NIAID global preparedness efforts. Other examples of platform technologies include screening systems, *in vitro* safety testing, protein expression methodologies, manufacturing technologies, and chemical synthesis designs. The potential to rapidly apply such platform methods to developing new MCMs, particularly when pursued on a global scale, will considerably shorten and streamline the process of countermeasure development.

NIAID will also continue to support and advance technology transfer agreements that attract potential industry partners and shorten the timeframe from discovery to licensure of effective public health tools, such as diagnostics, vaccines, and biologics. Appropriate technology transfer agreements serve to protect publicly funded discoveries while also accelerating the time to commercial availability.

Infrastructure

Preclinical and Clinical Research Infrastructure

Appropriate research infrastructure capacity will enable effective pandemic preparedness and rapid response research. The enhancement and expansion of dedicated USG owned or funded pre-clinical testing facilities with Animal Biosafety Level 3 (ABSL-3) and ABSL-4 capacity can boost the testing of promising candidate drugs and vaccines and mitigate delays in the event of a pandemic.

Global clinical trial networks that provide research capacity for all patient populations against emerging threats are essential to an effective research response. Preparedness includes leveraging and expanding existing domestic and international outpatient and inpatient clinical trial sites, enhancing on-site expertise, and developing the clinical research infrastructure needed to evaluate countermeasures and rapidly respond to infectious diseases. For example, the COVID-19 Prevention Network was a successful example of leveraging several existing clinical trial networks originally established for other purposes, to test vaccines and mAbs quickly and effectively against SARS-CoV-2. Internationally, other networks also were able to adapt to undertake coordinated COVID-19 clinical studies.

Pilot cGMP Manufacturing Capacity and Process Development

Preparedness efforts will require adequate capacity for process development and pilot Current Good Manufacturing Practice (cGMP) manufacturing of MCMs against prototype and priority pathogens. By manufacturing product and conducting Phase I/II trials, NIAID aims to attract industry partners and shorten the timeframe from scientific discovery to licensure to application of effective public health tools.

Regulatory Science and Strategy Infrastructure

Pandemic preparedness efforts will require close interaction with regulatory authorities and USG partners, particularly the FDA, as well as an understanding of foreign regulatory agencies and processes. Regulatory coordination will ensure that all NIAID-wide pandemic preparedness efforts are harmonized to the extent possible.

Coordination and Communication

Effective coordination and communication are central to effective preparedness research efforts and requires close collaboration both among the NIH ICs and with external partners in the United States, other countries, international organizations, and biomedical research-oriented philanthropies. The NIAID Pandemic Preparedness Plan will ensure that all internal NIAID pandemic preparedness efforts, encompassing intramural and extramural programs, are harmonized and supported by the effective mobilization of logistical, administrative, and technical resources. NIAID will also actively collaborate and integrate its efforts with similar ones undertaken by other USG entities, including CDC, USAID, DoD, and other agencies. Through multiple mechanisms, NIAID also will coordinate its programs with foreign government entities; international organizations, including WHO, the Global Fund, CEPI, GAVI, BMGF, and others; and domestic and international academic, private sector, and NGO entities.