

# Prototype Pathogen Approach for Vaccine and Monoclonal Antibody Development: A Critical Component of the NIAID Plan for Pandemic Preparedness

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Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) emerged 20 years ago, presaging a series of subsequent infectious disease epidemics of international concern. The recent emergence of SARS-CoV-2 has underscored the importance of targeted preparedness research to enable rapid countermeasure development during a crisis. In December 2021 the National Institute of Allergy and Infectious Diseases (NIAID), building upon the successful strategies developed during the SARS-CoV-2 response and to prepare for future pandemics, published a pandemic preparedness plan that outlined a research strategy focused on priority pathogens, technology platforms, and prototype pathogens. To accelerate the discovery, development, and evaluation of medical countermeasures against new or previously unknown pathogens of pandemic potential, we present here a strategy of research directed at select prototype pathogens. In this manner, leveraging a prototype pathogen approach may serve as a powerful cornerstone in biomedical research preparedness to protect public health from newly emerging and reemerging infectious diseases.

**Keywords.** pandemic preparedness; prototype pathogen; vaccine; monoclonal antibody; platform technologies.

The last 20 years have witnessed the unprecedented emergence and rapid spread of infectious diseases of global health importance, accelerated by international travel, human conflict, natural disasters, and changes in the environment and land use [1, 2]. Over the past 2 decades, the National Institute of Allergy and Infectious Diseases (NIAID), a component of the United States National Institutes of Health (NIH), has launched research responses against emerging and reemerging pathogens, including severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), pandemic influenza A viruses, Ebola virus, chikungunya virus, Middle East respiratory syndrome coronavirus (MERS-CoV), Zika virus, and SARS-CoV-2. In September 2021, the US Government, recognizing the continued threat of pandemics, announced the American Pandemic Preparedness Plan: Transforming Our Capabilities (AP3), which outlines an investment across the government for a rapid response to future pandemics [3]. Likewise, in December 2021, NIAID released its

Pandemic Preparedness Plan detailing a vision for prioritizing research efforts to better prepare for the next pandemic threat [4].

## METHODS

### NIAID Approach to Pandemic Preparedness

The NIAID Pandemic Preparedness Plan, aligned with several goals of the AP3, prioritizes research in 3 areas: priority pathogens, enabling technologies, and prototype pathogens [4, 5]. Priority pathogens include recognized viruses that are anticipated to threaten public health (eg, influenza virus, SARS-CoV-2, Ebola virus). Enabling technologies encompass innovations to rapidly advance and easily deliver safe and effective interventions. These technologies include vaccine platforms like messenger RNA (mRNA) and recombinant virus vaccines, new adjuvants to enhance long-term protective immunity, and improved methods to thermostabilize vaccines. Additional routes of administration such as intranasal or intradermal vaccines may be important for generating strong immune responses at mucosal and other key sites of pathogen exposure or for lowering dosage, respectively. These technologies have the potential to make vaccines more accessible to developing nations, due to lack of requirement for cold chain storage, and attractive due to noninvasive delivery [6, 7]. Prototype pathogens are representatives from viral families with pandemic potential, the characterization of which is used to develop generalizable medical countermeasure (MCM)

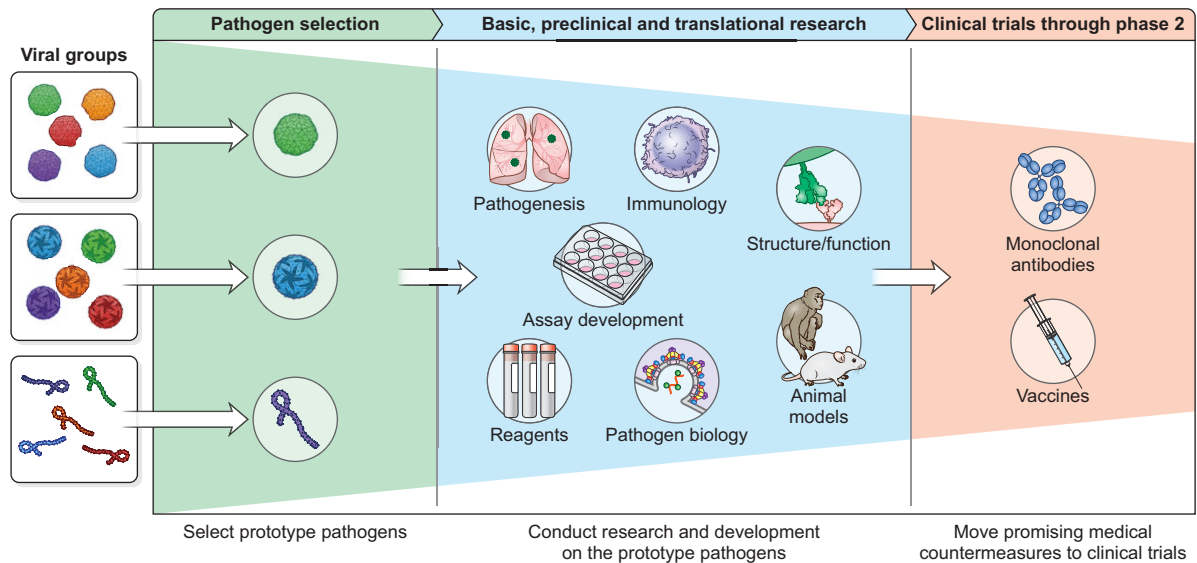
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**Figure 1.** National Institute of Allergy and Infectious Diseases (NIAID) prototype pathogen approach: prototype selection, research and development, and clinical trials. Prototype pathogens (one or a few from a family) will be selected for additional study from viral families of concern with input from subject matter experts. Once selected, characterization of the prototypes will be performed to understand pathogen biology, examine host immunity, develop animal models, and study pathogenesis, among other research and development efforts. Promising medical countermeasures (MCMs)—developed based upon viral characterization—will move into clinical trials. The goal of the prototype pathogen strategy is to use a generalizable MCM approach that can be applied to other members of the same viral family. Initial prototype pathogens were selected at a NIAID workshop held in November 2021. Figure adapted from the NIAID Pandemic Preparedness Plan [4].

solutions (eg, vaccines, monoclonal antibodies [mAbs], therapeutics) that are immediately applicable to the selected prototype and readily adaptable to other viruses in the same family. In some cases, viruses can be selected as both prototype and priority pathogens.

In addition to the 3 research areas above, the NIAID Pandemic Preparedness Plan includes developing diagnostics, advancing antiviral therapeutics through the NIAID Antiviral Program for Pandemics, addressing infrastructure needs, expanding preclinical and clinical testing capacity, and enhancing communication between stakeholders [4, 8]. This article, however, will focus only on the prototype pathogen approach and how it can be applied to developing MCMs against future emerging and reemerging public health threats. MCMs herein will refer to vaccines and mAbs.

Whereas vaccines aim to reduce transmission, morbidity, and mortality through direct immunization, mAbs can be administered as passive immunity for prophylaxis or treatment. These MCMs are critical, and their rapid deployment can contain an outbreak prior to epidemic or pandemic expansion.

### Prototype Pathogen Approach

To prepare for the emergence of infectious disease threats, existing and unknown, the NIAID prototype pathogen approach prioritizes basic, translational, and clinical research on selected viruses with a goal of developing MCM strategies that can be applied broadly to viruses in the same family

(Figure 1). Viruses in each family are genetically and functionally related, often sharing many characteristics such as mechanism of entry, genomic arrangement, replication cycle, and pathogenic mechanisms of disease. The validity of the prototype pathogen approach has been highlighted by the rapid response to the coronavirus disease 2019 (COVID-19) pandemic. Research conducted over the past 20 years on coronavirus entry mechanisms and spike proteins (mostly on SARS-CoV-1 and MERS CoV), as well as advances in mRNA vaccine platform technologies, enabled the development and authorization of COVID-19 vaccines at unprecedented speed.

Research on prototypes from viral families with pandemic potential will focus on: (1) characterizing aspects of pathogen biology and host-pathogen interactions, including the induction and maintenance of protective immunity; (2) understanding pathogenesis; and (3) developing MCMs against these prototypes through safety and proof of concept clinical trials. The goal of the prototype pathogen approach is to develop a generalizable MCM strategy that can be applied to other viruses in the same viral family, enabling the rapid development of MCMs and shortening timelines between pathogen outbreak and regulatory authorization if a virus with similar properties emerges. The goal is not to develop one specific MCM for each virus within a family, nor is it to develop a single vaccine that elicits heterologous protection against all members of the family.

### **Enabling a Prototype Pathogen Approach Towards MCM Development**

To apply the prototype pathogen approach for MCM development, an enhanced research portfolio is required to obtain fundamental and translational knowledge. This will entail new insights into many facets of the biology, structure, immunology, and pathogenesis of viruses targeted for study, as described below.

### **Basic Research to Study Viral Structures for MCM Development**

Understanding virion structure and entry mechanisms are critical for developing effective MCMs. Components of virus entry mechanisms are frequently targeted by protective antibody responses and are attractive targets for MCM design. Both enveloped and nonenveloped viruses have evolved multiple strategies for penetrating the membranes of target cells. Enveloped viruses are decorated with viral entry proteins that mediate attachment to cells and promote fusion of viral and host membranes [9–12]. The capsids of nonenveloped viruses contain surfaces critical for attachment to cells and uncoating [13]. Understanding similarities between entry mechanisms may identify new approaches for vaccine design and aid in developing reagents for therapeutic antibody discovery applicable to other viral family members.

The study of structural heterogeneity and dynamics of virions as they relate to their function and pathogenesis will be included in the research portfolio for the prototype pathogen approach. Virions may be pleiomorphic, with important consequences for entry, pathogenesis, and immune recognition. Notable examples are flaviviruses and picornaviruses [14, 15]. Sequence diversity within fusion proteins or accessory proteins incorporated into virions may also alter the structure(s) and antigenicity of the viral fusion machinery impacting antibody recognition. Understanding this complexity will require extensive exploration of the structures of virions and their viral proteins, and factors governing epitope presentation of multiple viruses within viral families of pandemic potential. Strategies enabling the characterization of virion structures and viral proteins, such as x-ray crystallography, nuclear magnetic resonance imaging, cryogenic electron microscopy, and computational modeling, are critical to pandemic preparedness and integral to the prototype pathogen approach.

Defining the structural consequences of sequence variation on antigenicity is critical to antigen design, to understanding immunity following infection and vaccination, and for developing immune assays. Stabilization of viral fusion or capsid proteins to reduce heterogeneity, increase rigidity, and to maintain conformations of proteins and virions in their functional state has shown promise as a strategy to elicit higher levels of protective neutralizing antibodies [16, 17]. High-resolution insights into virion structures and viral surface proteins will inform protein engineering approaches needed to achieve the optimal design of vaccine antigens.

### **Immunity and the Discovery of Protective Antibodies**

Protective antiviral immunity relies on components of cell-intrinsic, innate, and adaptive immune responses. Deeper insights into the contribution of multiple immune arms and the role of immune memory to protect against viruses of high pandemic potential are critical for understanding pathogenesis, identifying relevant animal models of disease, establishing correlates of protection, understanding durability of immunity, and developing MCMs. Studies to decipher the contributions of these systems and crosstalk among them are a critical element of the NIAID prototype pathogen approach.

The innate immune response can control, in part, aspects of virus infection, tropism, and disease. Innate immune-deficient mouse strains are often highly permissive to infection. While imperfect, their use has enabled rapid advances in the study of viral pathogenesis, immunity, and MCM evaluation. The contributions of innate immune cells, including myeloid subsets and innate lymphoid cells, during primary and memory antiviral responses are critical areas for future study.

It is also essential to understand the adaptive immune response to infection. T- and B-cell responses contribute variably to protection from viral infection and viral clearance. T cells are critical for resolution of pathogens and can directly clear cells that become virally infected. T cells also contribute to protection through the production of antiviral cytokines and chemokines and by providing help for the humoral immune response. The identification of T-cell epitopes in viral proteins directly informs antigen design.

B-cell lineage cell-derived (B cells, plasmablasts, and plasma cells) antibodies contribute to protection from viral infection and disease by directly neutralizing virions and coordinating effector functions of cells of the immune system. A comprehensive analysis of the targets of the antibody response provides important insight into immune protection and mechanisms of immune escape, including the impact of viral diversity. The surfaces of prioritized pathogens recognized by antibodies have been studied using multiple approaches, including structural biology [15–21]. Efforts to comprehensively catalog the specificity of antibodies produced from B cells following infection or vaccination is a powerful approach supported by continued advances in single-cell analysis, high-throughput sequencing, computational and structural biology, and protein engineering. The discovery of new human mAbs with therapeutic potential, enabled by the prototype pathogen approach, will advance pandemic preparedness.

### **Animal Models to Enhance MCM Development**

Animal models that capture relevant mechanisms of human disease and transmission are desired and play a critical role in the evaluation of viral antigens. Understanding the viral antigen characteristics and immune mechanisms that make prototype vaccines effective is critical for demonstrating

experimentally that a vaccine design concept will be effective when applied to other members of the same viral family. Animal models also are important in assessing vaccine platforms, vaccine delivery formats, routes of administration, and delivery schedules, as well as establishing immune correlates of protection from infection or disease. Efforts to standardize these animal models using a diverse, yet representative, panel of viral strains will greatly accelerate the comparison and downselection of MCM candidates.

The first downselection of vaccine and mAb candidates occurs during the preclinical phase of development when small animal studies indicate a reasonable expectation of benefit. These studies also ensure a standardized measurement of safety. In later stages, appropriate animal models that utilize comparable routes of infection, inoculum doses, and display of clinical symptoms as observed in humans are necessary for the downselection of MCMs for further development. Identifying vaccine-induced correlates of protection in these later stages of preclinical development is an important step for moving vaccine candidates forward.

#### **MCM Platform Considerations**

The NIAID Pandemic Preparedness Plan focuses on exploring platforms beyond standard approaches to seek MCMs that are safe, efficacious, and rapidly deployable. Ideal vaccine candidate development includes parallel research of basic target-antigen design and ready-to-use pathogen-agnostic platforms. While the choice of platform (and delivery route) will impact the timeline and type of immune response elicited, a successful preparedness strategy must (1) focus on careful antigen design of research candidates that might result in highly efficacious and scalable MCMs; and (2) consider anticipated safety risks—especially important when moving quickly to population-scale deployment. As detailed above, the study of virus target proteins, informed by virology and immunology, along with deliberative, structure-based vaccine design approaches that incorporate an understanding of host immunity, are essential to the success of new MCMs [18, 19].

An iterative process of improving the design of vaccine prototypes through preclinical testing, process development, pilot manufacturing, regulatory strategy, and clinical testing is integral for pandemic preparedness planning and MCM development. This process is also essential for generating reagents, optimizing immune assays, and establishing animal models and other pathogen-specific tools needed for the development of candidate MCMs [20, 21].

#### **Clinical Assessment of Candidate MCMs**

Clinical evaluation of an investigational new product is the final phase in the integrated process for developing safe and effective MCMs. Maintaining 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 are essential preparedness activities. This organized effort not only ensures that experienced clinical trialists design and run harmonized protocols that enable the study and comparison of countermeasures, but it also allows the incorporation of key features to the clinical plan, such as representation across the lifespan and inclusivity of vulnerable demographic groups. As learned throughout the COVID-19 pandemic, underlying health conditions, such as diabetes and obesity, play a detrimental role in disease outcomes. These confounding conditions must be kept in mind while studying pathogenesis and in the context of MCM development. Incorporation of experienced clinical sites into an international network directly contributes not only to the successful and timely evaluation of promising candidates, but also encourages the acceptance of authorized countermeasures by underrepresented communities and populations sometimes excluded from initial clinical evaluations. In this regard, the NIAID pandemic preparedness strategy will facilitate the conduct of phase 1/2a clinical trials in human subjects to evaluate safety and show proof of concept of candidate MCMs. When the candidate MCM is applicable to both prototype and priority pathogens, NIAID will work with other government agencies, such as the Biomedical Advanced Research and Development Authority (BARDA), nongovernment organizations, or industry to further develop these candidates. In some cases, there may not be enough transmission of virus in the environment to evaluate efficacy; therefore, other regulatory pathways for licensure (ie, the animal rule, in silico clinical trials) may need to be utilized [22, 23]. For nonpriority pathogens, the knowledge gained through study of the prototype pathogen will be quickly applied to emerging pathogens.

## **RESULTS**

### **Prototype Pathogen Identification**

#### *Viral Family Selection*

Resource and time constraints prevent the fundamental and translational discoveries required to support MCM development for each of the thousands of viruses within the approximately 26 distinct viral families known to infect humans [24, 25]. Therefore, application of the prototype pathogen approach to gain extensive knowledge of select pathogens within viral families of concern is necessary. NIAID determined on which viral families to focus prototype pathogen efforts by sorting them into 2 categories: families with a substantial likelihood to cause pandemics and families with moderate to low pandemic potential. Next, each viral family was evaluated according to the research landscape, known MCMs, and historical research support levels. Families that had high pandemic potential, insufficient knowledge and MCMs, and low to moderate research support were considered the highest priorities. [Figure 2](#) shows

		Pandemic potential	
		Low/Moderate	High
Existing resources or countermeasures	High	<ul style="list-style-type: none"> <li>• <b>Hepadnaviridae</b></li> <li>• <b>Papillomaviridae</b></li> <li>• <b>Poxviridae</b></li> <li>• Retroviridae</li> </ul>	<ul style="list-style-type: none"> <li>• Coronaviridae*</li> <li>• Orthomyxoviridae*</li> </ul>
	Low/Moderate	<ul style="list-style-type: none"> <li>• Adenoviridae*</li> <li>• Anelloviridae</li> <li>• Arteriviridae</li> <li>• Astroviridae</li> <li>• Bornaviridae</li> <li>• Caliciviridae</li> <li>• Hepeviridae</li> </ul>	<ul style="list-style-type: none"> <li>• Herpesviridae</li> <li>• Parvoviridae</li> <li>• Picobirnaviridae</li> <li>• Pneumoviridae</li> <li>• Polyomaviridae</li> <li>• Reoviridae</li> <li>• Rhabdoviridae*</li> </ul>
			<ul style="list-style-type: none"> <li>- Bunyavirales</li> <li>• Arenaviridae</li> <li>• Hantaviridae</li> <li>• Nairoviridae</li> <li>• Peribunyaviridae</li> <li>• Phenuiviridae</li> </ul>
			<ul style="list-style-type: none"> <li>• Filoviridae*</li> <li>• Flaviviridae*</li> <li>• Paramyxoviridae*</li> <li>• Picornaviridae*</li> <li>• Togaviridae</li> </ul>

**Figure 2.** Comparison of pandemic potential and countermeasures for viral families known to infect humans. Viral families were categorized as having either low/moderate or high pandemic potential and low/moderate or high levels of existing resources and countermeasures. Cross-comparison revealed 10 viral families with high pandemic potential and low/moderate existing resources or countermeasures upon which National Institute of Allergy and Infectious Diseases (NIAID) will focus its pandemic preparedness activities. \*Existing vaccine solutions for some viruses in that family; bold, potential vaccine solutions for the entire family; shaded box, viral families chosen for prototype pathogen selection.

the outcome of the cross-comparison resulting in the following 10 viral families from which to select prototype pathogens: Arenaviridae, Hantaviridae, Nairoviridae, Peribunyaviridae, and Phenuiviridae (Bunyavirales order); Filoviridae; Flaviviridae; Paramyxoviridae; Picornaviridae; and Togaviridae (lower right quadrant in [Figure 2](#)).

Although Orthomyxoviridae and Coronaviridae ([Figure 2](#) upper right quadrant) have extremely high potential for future pandemics and have been the causative agents for major outbreaks over the last few decades, they have been excluded from prototype pathogen approaches because they are considered priority pathogens. NIAID has allocated significant resources and developed expanded programs to understand these families and develop MCMs.

Viral families that appear in the upper left quadrant of [Figure 2](#) (low to moderate risk/high existing resources) were not included in the selected viral families because interventions already exist, the viruses are well studied, and significant funding has been allocated to those viral families. Viral families in the lower left quadrant of [Figure 2](#) (low to moderate risk/low to moderate resources) require additional study to better understand the risk they might pose for pandemic spread.

#### Expert Input on Prototype Pathogen Selection

In November 2021, NIAID hosted the “Workshop on Pandemic Preparedness—The Prototype Pathogen Approach to Accelerate Medical Countermeasures—Vaccines and Monoclonal Antibodies.” The objective of the workshop was to introduce the NIAID Pandemic Preparedness Plan and obtain feedback from the scientific community on selection of

prototype pathogens within the prioritized viral families. Before the workshop, subject matter experts on viral families from academia, government, and industry were assembled to review the NIAID prototype pathogen approach, summarize the basic and translational research landscape, identify research and intervention gaps, assess current preclinical and clinical vaccine and mAb candidates, and propose prototype pathogens.

During the workshop, each viral family working group presented their findings followed by a question-and-answer session. [Table 1](#) briefly describes the findings of each group. A more detailed, comprehensive review of the state of the science, including the identification of basic research gaps and models of disease, and a list of prototype pathogens and rationale for selection for each of the viral families, will be the subject of a separate publication.

#### Common Scientific Gaps and Challenges Across Viral Families

Subject matter experts identified key scientific gaps and challenges for their respective viral families ([Table 1](#)). Many of the challenges highlighted were common among all families ([Figure 3](#)). These cross-cutting challenges will be a focus of future research as they are vital to the success of the NIAID pandemic preparedness strategy and overall prototype pathogen approach. Some of these challenges are listed below.

#### Basic Research

Structures of the viral entry proteins of viruses that represent many of the selected families have been characterized. A more extensive survey of the structures of viral entry proteins

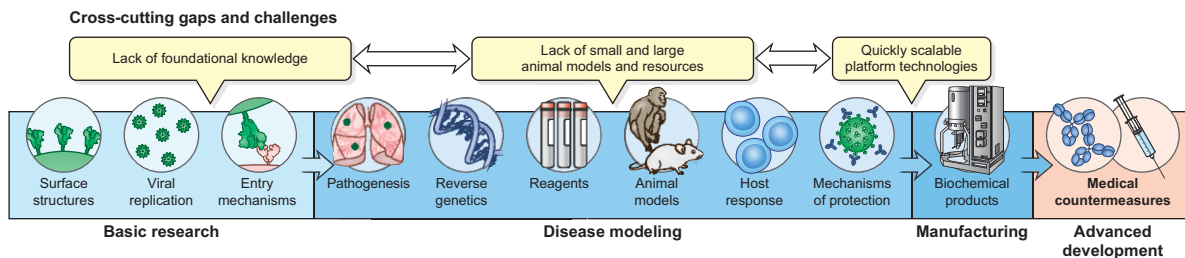


**Table 1. Viral Families of Concern, Prototype Pathogens, and Scientific Gaps**

Family	Prototype Pathogens	Rationale for Prototypes	Scientific Gaps/Unknowns	Countermeasures <sup>a</sup>			
				mAb		Vax	
				Pre	Clin	Pre	Clin
<b>Bunyavirales families</b>							
Arenaviridae	Lassa fever virus	Endemic in West Africa; high disease burden and lethality rate	Human receptors; mechanisms of immune protection and vaccine antigen optimization; contemporary isolates	+	-	+	+
Hantaviridae	Junin virus Andes virus	Expanding endemic range Human to human transmission; severe pulmonary disease or hemorrhagic fever; lethal	Role of viral glycoproteins; reverse genetics systems; animal models	++	+	+	-
Nairoviridae	Sin Nombre virus Hantaan virus	Rodent to human transmission; severe disease Less lethal; BSL-3					
Peribunyaviridae	CCHFV Hazara virus La Crosse virus	Endemic with frequent outbreaks; severe disease and mortality; tick borne Surrogate that can be studied at BSL-2 Encephalitic disease; endemic in United States	Viral-host interactions; host receptors and viral glycoprotein structures; cell and animal models Early infection; entry mechanisms and viral-host protein interactions; diverse pathology; cell and animal models	+	+	+	-
Phenuiviridae	Cache Valley virus RVFV SFTSV PTV	Congenital disease Transmitted by mosquito (RVFV), tick (SFTSV), and sand-fly (PTV); wide range of clinical manifestations; endemic	Entry receptors; cell and animal models beyond RVFV	++	+	+	-
<b>Other families</b>							
Filoviridae	Ebola virus	Human disease; cross-protective vaccine platforms	Viral reservoirs; mechanisms of pathogenesis; viral persistence, and sequelae; alternative models	++	++	++	++
Flaviviridae	West Nile virus	Encephalitic disease; mosquito transmission	Detailed viral structures; cell receptors; role of immunity in protection from infection/sequential infection/cross protection; ADE; improved models	++	+	++	++
<b>Dengue serotype 2 virus</b>							
Hemorrhagic disease; mosquito transmission							
<b>Tick-borne encephalitis virus</b>							
Encephalitic disease; tick transmission							
Paramyxoviridae	Measles virus Human parainfluenza virus 1/3 Cedar virus Canine distemper virus	Prototypes selected from each genera within the family; viruses infect multiple cell types, exhibit a wide host range, can be found in animal reservoirs, and have respiratory transmission	Cell entry; transmission dynamics; mechanisms of persistence; antigenic targets; host immunity to infection; cell and animal models	+	+	+	+
Picornaviridae	Enterovirus A71	Endemic in SE Asia; reagents available	Mechanisms of immune protection, role of B and T cells, and innate immunity; antigenic structures; animal models	+	+	+	+
<b>Respiratory pathogen, rapid evolution</b>							
Enterovirus D68							
<b>Respiratory pathogen; well studied</b>							
Rhinovirus C							
<b>Respiratory pathogen; zoonotic</b>							
Echovirus							
<b>Arthritogenic; high burden of disease</b>							
Togaviridae	Chikungunya virus	Arthritogenic; high burden of disease	Early infection events; pathogenesis; optimal antigen design; and role of T cells in protection	++	++	++	++
<b>Encephalitic; widespread zoonotic infection</b>							
VEEV							

Abbreviations: ADE, antibody-dependent enhancement; BSL, biosafety level; CCHFV, Crimean-Congo hemorrhagic fever virus; mAb, monoclonal antibody; PTV, Punta Toro virus; RVFV, Rift Valley fever virus; SFTSV, severe fever with thrombocytopenia syndrome virus; Vax, vaccine; VEEV, Venezuelan equine encephalitis virus.

<sup>a</sup>Countermeasure key: poorly understood (-), limited knowledge (+), good body of knowledge (++), well-defined (+++); evaluated preclinically (Pre), evaluated clinically (Clin).



**Figure 3.** Common gaps along the research and development continuum that inhibit the development of medical countermeasures. Subject matter experts identified several research gaps within the 10 viral families of pandemic concern that were common among all the families. Addressing the challenges and closing those gaps will advance the development of medical countermeasures.

and their arrangement on virus particles will provide insight into the heterogeneity and dynamics of virions, consequences of viral variation, interactions with host cell receptors, and the display of antibody epitopes. The identification of host receptors and greater insight into entry mechanisms will also advance strategies for the development of MCMs. Information related to viral pathogenesis, host immunity, and correlates of protection from virus infection will provide critical fundamental knowledge and inform the identification of the most appropriate models for MCM preclinical development. The rational design of vaccine antigens and their optimization to elicit protective immune responses will be heavily dependent on this foundational research.

#### **Disease Models**

Disease models to evaluate interventions and appropriately screen candidates are required. Relevant *in vitro* and organoid models of infection, as well as robust small and large animal models that recapitulate human disease, are critical. The need for increased availability of nonhuman primates, especially in high biosafety level laboratories, also must be addressed. Complementary to nonanimal and animal models are appropriate reagents to assess virologic and immunologic responses.

#### **Viral Isolates**

Comparative research studies for both viral characterization and MCM testing will necessitate the adoption and use of appropriate, contemporary viral isolates that have been well characterized. Some laboratories are using isolates collected decades ago because new stocks have not been derived or deposited into resource databases. Collecting viral isolates currently circulating in humans, defining the sequence of the unpassaged clinical isolate, propagating in appropriate primary cell lines, and then depositing them into NIAID repositories will make them available to the entire scientific community.

#### **Biocontainment Facilities**

Many of the identified prototype pathogens require increased biosafety level containment facilities (ie, biosafety level 3 or 4

laboratories) to conduct research studies. In addition to physical space needs that meet the demand for these facilities, it is necessary to develop and sustain a workforce with the specialized skills to safely conduct preparedness research in high containment facilities.

#### **Contemporary Design Approaches and Platform Technologies**

Over a period of decades, highly effective vaccines have been developed and licensed for some viral families even without a detailed understanding of basic virology or immunology. However, some historically effective approaches to vaccine development (eg, live-attenuated or formalin-inactivated vaccines) are not well suited for adaptation to pathogens in the same family, rapid development, scaled up manufacturing, or authorization and deployment during a pandemic response. Newer technologies using structure-based antigen design and protein engineering should be considered and applied to select currently available vaccine candidates for prototype pathogens. The continued development of new vaccine and mAb technologies is a NIAID priority.

## **DISCUSSION**

There are known viruses with pandemic potential for which state of the art vaccines or mAbs do not exist. To address this deficiency, the NIAID Pandemic Preparedness Plan describes a systematic approach that studies prototype pathogens from viral families with known pandemic potential to develop MCMs against emerging or reemerging viruses. This anticipatory approach will substantially increase our preparedness and enable more rapid movement of candidate MCMs into clinical trials should a response to an outbreak be necessary.

Pandemic preparedness is a complex effort that will require close coordination and collaboration among federal and international partners. To accelerate progress, it will be critical that partnerships are established before the onset of outbreaks and that plans to standardize and share data, samples, and protocols are developed in advance. Partners may include NIH and other components of the US government (eg, BARDA, Centers for

Disease Control and Prevention, Food and Drug Administration, Office of Science and Technology Policy, and Department of Defense); industry; the World Health Organization; and other international funders, including the Coalition for Epidemic Preparedness Innovation, the Bill and Melinda Gates Foundation, and Wellcome Trust; and other international government organizations.

The COVID-19 pandemic has demonstrated that emerging and reemerging infectious pathogens are a real and present threat to public health. Refocusing our research efforts and making strategic investments to enhance preparedness will be critical to mitigating and preventing future pandemics. The NIAID strategy for research on pandemic preparedness described here offers a clear and actionable roadmap toward this important goal.

## Notes

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