

# Expediting Development of Medical Countermeasures for Unknown Viral Threats: Proposal for a “Virus 201” Program in the United States

## Commentary

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Editor's Note, May 7, 2021: The proposed Virus 201 Program has been renamed the Disease X Medical Countermeasure Program.

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The COVID-19 pandemic has shown the devastating potential impact of new infectious diseases on the United States and the world. More than 104,000 Americans have already died, communities are shut down, and huge economic losses are occurring here and around the world. The profound effects of this pandemic should galvanize the US Congress to do everything in its power to prevent this from happening again. There are an average of 200 epidemics requiring international response each year, and the next fast-moving, novel infectious disease pandemic—“Virus 201”—could be right around the corner.

Recent global experience with severe infectious disease epidemics had triggered much interest in understanding the broader pandemic threat landscape. A substantial proportion of pandemic and biological threat preparedness activities were and are focused on list-based approaches that are in part based on pandemic influenzas of the past, historical biological weapons development programs, or recent outbreaks of emerging infectious diseases (eg, SARS, MERS, Ebola). But a list-based approach by its nature fails to account for unknown pathogens or those without historical precedent.

Given the severe potential public health consequences of pandemic events, the US government has a vital interest in developing and maintaining a flexible, rapid, and robust medical countermeasure capability. Anticipating the forms of microbial threats that might cause future pandemics can help strengthen preparedness and response capacities. A new approach to infectious disease countermeasures that is not exclusively anchored to a specific pathogen but reflective of addressing unknown threats, or Virus 201, would provide an enhanced response capacity and augment resilience to infectious disease emergencies.

While it is not possible to identify exactly what may cause the next pandemic, there are certain overarching and known principles that can help make predictions that can in turn guide preparations.

## **The Alchemy of a Pandemic Pathogen**

When a pathogen has the capacity to cause a pandemic, it will most likely possess several attributes that other microbes, capable of causing only sporadic or limited human infections, will lack. These traits can be divided into several categories: spread via respiratory transmission; capable of presymptomatic spread during the incubation period prior to symptom onset or asymptomatic spread; minimal preexisting immunity in the population; and a lack of effective therapies or vaccines. Currently, these traits are possessed by some but not all members of the microbial world but are common to viruses.

These traits can be mapped onto the approximately 2 dozen known viral families capable of infecting humans to delineate pandemic threats and to further narrow the list of potential pathogens with pandemic potential. Special attention should be given to viruses with this capacity in high-risk animal species, given the zoonotic nature of many high-consequence emerging infectious diseases.

## Countermeasures Against Virus 201

Our best defense against these pandemic pathogen threats are safe and effective medical countermeasures (MCMs). Such countermeasures may include:

- **Antivirals:** In the time before a vaccine is available, antiviral treatments must be developed and deployed to decrease complications, hospitalizations, contagiousness, and mortality. Novel antiviral therapies range from small molecules to monoclonal antibody–based products.
- **Vaccines:** Vaccines are the best solution to protecting people from novel viruses, but they usually take the longest to develop. Vaccine technologies have progressed in recent years to include several promising platform technologies that can be more quickly leveraged once a threat has been characterized.
- **Diagnostics:** Diagnostics are critical to identify people who have been exposed to or infected by a virus. In recent years, rapid and extensive diagnostic testing technology has been developed and commercialized.

However, the development of these life-saving products usually takes years, if not decades. If we wait until the next pandemic presents itself before turning to medical countermeasure development, we will find ourselves again in the same situation where we are today: working feverishly, setting aside other important medical countermeasure development projects, and throwing maximum resources to speed development and manufacture of COVID-19 Medical countermeasures.

When the next deadly pathogen emerges, the United States needs to have the ability to tap into ongoing technologies and platforms in which it has already strategically invested so that Medical countermeasures can be developed and deployed much faster. This will require sustained funding, ongoing programs, and technical staff dedicated to accelerating the development of Medical countermeasures for previously unidentified infectious disease threats.

## Virus 201 Antiviral Therapies

The US government should invest deeply in development of new antiviral therapies that would be effective against respiratory viruses. Currently, outside of anti-influenza antivirals, there is only one FDA-approved antiviral for the treatment of respiratory-spread viruses (ribavirin). Of the 6 FDA-approved influenza antivirals—amantadine, rimantidine, baloxavir, zanamivir, oseltamivir, and peramivir—all target influenza viruses specifically and have no activity outside influenza. Two influenza A–specific agents (amantadine and rimantadine) have been rendered virtually obsolete because of resistance. The other antiviral agent (inhaled ribavirin) is approved for the treatment of respiratory syncytial virus (RSV). It has very limited use due to poor efficacy and major toxicity concerns for both RSV and parainfluenza viruses, although oral formulations have begun to be used off-label.

There are currently no approved antivirals for any other respiratory-spread RNA viruses in the world. Remdesivir does possess an emergency use authorization (EUA) for the treatment of specific COVID-19 patients, and the often-toxic antiviral cidofovir has been used off-label for adenoviral infections.

Prioritization of antiviral compounds against the families of viruses that possess some degree of pandemic-relevant traits could lead to acceleration of drug development and (government and nongovernment) incentivizing programs. Such antiviral compounds would have an advantage over many other emerging infectious disease countermeasures: Viruses in these families exact a considerable toll in the form of community infections each year, so incentives in therapies aimed at these families of viruses could help spur development of therapies for routine infectious disease threats as well as novel pandemic threats.

An antiviral program could be divided into several functional components or arms:

1. Repurposing of existing antivirals: Take high-risk viral families (eg, paramyxoviruses) and screen existing and newly developed antiviral compounds against these viral family members. Artificial intelligence and machine learning tools can make this process faster.
2. Broad-spectrum antiviral development: Design antiviral compounds that may have an effect against high-risk viral families. Such antivirals may target a specific pathway shared by all family members in designated viral families. These compounds could then form the basis of a more specific product once a threat materializes.
3. Monoclonal antibody development: Assess high-risk viral families for their susceptibility to neutralization by monoclonal antibodies that could potentially be used for preexposure prophylaxis, treatment, and postexposure prophylaxis. Characterize the requisite antibody target, and develop the corresponding monoclonal antibody. Such antibodies would be trialed in animal models, with promising candidates advancing through existing development programs.
4. Immune modulation: Many immunomodulatory products are available that may have nonspecific effects that ameliorate common pathways leading to host damage. It would be greatly beneficial to fund research to understand the inflammatory cascade brought on by high-risk viral families (in animals and humans) and assess existing and potential immunomodulatory compounds for their ability to interrupt these processes. Such nonspecific measures may be able to decrease the morbidity and mortality of infection. In addition to immunomodulatory compounds, a Virus 201 program could develop nonspecific procedures or devices, such as apheresis for cytokines or a procedure akin to LPS hemoperfusion (used for bacterial septic shock), for similar use.

## **Virus 201 Vaccines**

New vaccine platform technologies (eg, messenger RNA, DNA, modified vaccinia ankara, adenoviral vectors) have advanced in recent years and are expected to enable more rapid response to a new virus. Platform technologies are a sustainable pluripotent infrastructure that can be applied to vaccines with minimal added financial risk, thereby diminishing both costs and time of vaccine development. These platforms are currently being leveraged to develop COVID-19 vaccines.

In general, for both platform and traditional vaccine approaches, virus families thought to possess pandemic potential should be studied to determine which viral antigen confers immunity in animal models as well as in humans (because members of a viral family already infect humans and cause mild disease, as was the case with coronaviruses).

As applied to Virus 201, platform vaccine technologies, specifically viral-vector and cell-line based (eg, baculovirus expression systems), could be evaluated for their adaptability to various viral targets in specific families. With nucleic acid platforms, by contrast, identifying the immunogenic viral gene product might be sufficient.

It is important that the traditional approach to vaccine R&D not be entirely supplanted by platform approaches. While platform-based approaches might be the future of vaccine development for many targets, there are infectious disease targets that currently exist or may emerge for which a traditional vaccinology approach might be most likely to succeed.

## **Virus 201 Diagnostics**

Future pandemics will probably appear as familiar clinical syndromes, such as pneumonia, meningitis, encephalitis, or sepsis, the final common pathway for many life-threatening illnesses. In the United States, when these clinical syndromes occur, the specific microbiological etiology is not determined in about half. Reasons for this include clinicians' lack of familiarity with diagnostic tools, lack of clarity around reimbursement in clinical settings, and regulatory challenges to using these tools for surveillance purposes when they are not used for primary clinical reasons. On the other hand, both clinicians and patients do want to know with more precision what causes infectious diseases, so there is potential to change the situation.

In addition, the gap in diagnostic acuity serves as a barrier to the development of Medical countermeasures. For example, if it turns out that 10% of respiratory infections in the country are caused by virus Z, but no one knows that it is causing so much morbidity, then there is no drive to develop countermeasures for it. If the full extent of virus Z is known, then that in itself may create more push for development of countermeasures. By understanding the true burden of specific microbes and facilitating a greater appreciation of their prevalence, the development of Medical countermeasures

such as vaccines and antivirals for these viruses could be spurred. These Medical countermeasures may be of great value, as many pathogens, such as respiratory viruses, are situated in groups that include potential pandemic pathogens. Additionally, lurking in the biological “dark matter” inciting these infections could be a novel pathogen or an old pathogen behaving differently.

The lack of diagnostic acuity is not for a want of technologies. In recent years, several highly sophisticated technologies have entered the market, and they offer the ability to increase sensitivity of diagnostic testing in a pathbreaking manner. By employing technologies such as whole genome sequencing, multiplex polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), mass spectrometry, and magnetic resonance, we could close the knowledge gap of unknown etiologies and greatly improve our early warning of a potentially severe pandemic.

Pathogen-agnostic diagnostics are now available through next-generation sequencing providers. These products can test blood samples for hundreds of pathogens. However, these technologies—which largely already exist and have regulatory approval—are not being applied in a systematic manner for Virus 201 readiness. A Virus 201 Medical Countermeasures Program could leverage these technologies.

## **A Virus 201 Medical Countermeasures Program Is Needed**

The United States must set an ambitious goal of rapidly developing Medical countermeasures for novel or unknown threats in months, not years. Innovative technologies, outside-the-box thinking, and game-changing science must be harnessed to meet this goal.

A new dedicated Virus 201 strategy, program, and funding must be created to achieve this goal through the US Department of Health and Human Services (HHS) Biomedical Advanced Research and Development Authority (BARDA) and the Department of Defense (DOD) Joint Program Executive Office for Chemical and Biological Defense (JPEO). This initiative should not compete with or cannibalize other important MCM development efforts focused on specific, known threats, and it should involve other innovative agencies, including the Defense Advanced Research Projects Agency (DARPA) and In-Q-Tel.

An unknown pathogen can affect both military personnel and the American public. DOD and HHS investment strategies should be coordinated through the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), with DOD taking the lead on products targeted to protect young, healthy military personnel, and HHS leading on other products needed to protect the diverse American public, including children and other vulnerable populations. The PHEMCE must also ensure collaboration with DARPA and In-Q-Tel.

A new congressional appropriation of \$1 billion, divided equally between HHS and DOD, should be provided to enable these agencies to initiate a robust and coordinated strategy to accomplish this goal before the next virus threatens the globe. Specifically, an additional \$500 million should be provided to BARDA and \$500 million to JPEO to implement these initiatives. Since Virus 201 medical countermeasures may not have a commercial market that drives private sector investment, it is essential that a sustainable public-private partnership model and dedicated funding be created to share the development risk, incentivize development of new Medical countermeasures, and invest in faster capabilities to respond to potential pandemics.

## **Conclusion**

As COVID-19 has demonstrated, new deadly viruses can spread quickly and easily around the globe, causing significant loss of life and economic downturn. With nearly 200 epidemics occurring each year, the next fast-moving, novel infectious disease pandemic—Virus 201—could be right around the corner. It still takes too long to develop novel antivirals, vaccines, and diagnostics through existing programs at HHS and DOD, which are primarily directed toward specific, known, high-priority health security threats. The United States must set an ambitious goal of rapidly developing and deploying Medical countermeasures for novel or unknown infectious disease threats in months, not years. Therefore, Congress should fund a new dedicated Virus 201 Medical Countermeasures program at BARDA and JPEO, coordinated through the PHEMCE.





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