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Viewpoint

COVID-19

The COVID-19 pandemic of acute respiratory disease caused by SARS-CoV-2 coronavirus (CoV) is an unparalleled event that harkens back to days before viruses could be seen or understood. HIV-1 arose as a regional zoonotic disease during the last century and evolved into a global crisis of enormous proportions; it was nearly universally fatal, but its global spread and disease progression were relatively slow, and it was perceived as being more escapable. More recent outbreaks, such as Ebola in West Africa and Eastern Congo and MERS-CoV in the Middle East were characterized by high mortality rates and rapid spread, but remained relatively contained regionally, with only episodic global spread. The arboviruses, Zika and chikungunya, caused devastating disease with long-lasting effects, but did not cause high mortality and were geographically limited by the range of their vectors. During the last century, the world has endured threats from avian influenza and pandemic influenza, but neither led to shutting down of society to the extent experienced with COVID-19. Uniquely, COVID-19 is caused by a newly discovered CoV strain and part of a virus family that many people had not heard of before, has substantial human-to-human transmission through respiratory secretions, has spread globally within a matter of weeks, affects individuals from all levels of society and status, and has a high enough morbidity and mortality [...]

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The COVID-19 pandemic of acute respiratory disease caused by SARS-CoV-2 coronavirus (CoV) is an unparalleled event that harkens back to days before viruses could be seen or understood. HIV-1 arose as a regional zoonotic disease during the last century and evolved into a global crisis of enormous proportions; it was nearly universally fatal, but its global spread and disease progression were relatively slow, and it was perceived as being more escapable. More recent outbreaks, such as Ebola in West Africa and Eastern Congo and MERS-CoV in the Middle East were characterized by high mortality rates and rapid spread, but remained relatively contained regionally, with only episodic global spread. The arboviruses, Zika and chikungunya, caused devastating disease with long-lasting effects, but did not cause high mortality and were geographically limited by the range of their vectors. During the last century, the world has endured threats from avian influenza and pandemic influenza, but neither led to shutting down of society to the extent experienced with COVID-19. Uniquely, COVID-19 is caused by a newly discovered CoV strain and part of a virus family that many people had not heard of before, has substantial human-to-human transmission through respiratory secretions, has spread globally within a matter of weeks, affects individuals from all levels of society and status, and has a high enough morbidity and mortality to overwhelm our health care systems. Therefore, it has galvanized public interest in pandemic threats as no other virus has before.

New technologies have revolutionized vaccinology

The COVID-19 pandemic is reminiscent of times before the development of vaccines

for smallpox, measles, polio, and influenza, when outbreaks spread rapidly and unexpectedly, causing high mortality, especially in susceptible subpopulations. Tremendous individual efforts and scientific breakthroughs leading to the development and application of vaccines over the last 70 years have resulted in control of those diseases and others. This era could be described as a period of responsiveness that followed a long history of defenselessness against viral diseases. While the number and frequency of pandemic threats seem to be escalating, there has also been a rapid accumulation of new technologies during the last ten years. These advances allow improved precision in vaccine design and more rapid manufacturing timelines. Leveraging these new tools, it is time to transition into an era of preparedness characterized by a greater reliance on established biological principles and engineering concepts and less dependence on empiricism.

In William Foege's personal history of the smallpox eradication effort, *House on Fire* (1), he begins with the following metaphor to describe ring vaccination strategies used to control and eradicate smallpox: "If a house is on fire, no one wastes time putting water on nearby houses just in case the fire spreads. They rush to pour water where it will do the most good — on the burning house." With the advent of the COVID-19 pandemic amidst concerns about melting glaciers, wildfires out of control, and other emerging virus threats, it feels like not just the house, but our world is on fire. We believe bringing more order and hope to the inevitability of repeated pandemic threats will require a systematic and proactive technology-based approach. Using Foege's analogy of the burning house, this new approach would be the equivalent of

building homes with flame-resistant material and installing fire alarms and sprinkler systems. Improved pandemic preparedness could be achieved by proactively managing emerging virus threats focused on four discreet activities using currently available tools: (a) discovery and surveillance, (b) targeted basic research, (c) translational research and product development, and (d) clinical trial infrastructure and deployment capacity.

Defining the scope of emerging virus threats through discovery

Using next-generation sequencing technology to improve virus discovery and surveillance efforts, we could fill in what could be referred to as the "periodic table of viruses" and define the virome of potential viral pathogens. The two major pathways from which new viruses emerge are zoonotic and vector borne. Knowing this, targeted efforts to identify new viruses in common mammalian reservoir hosts, such as bats and rodents, and in potential intermediate hosts, such as domesticated animals and primates, would reveal current and future potential threats. In parallel, systematic screening of common vectors such as mosquitoes and ticks for new viruses within viral families known to infect humans should be done. The investment in sequencing facilities distributed throughout the world concentrated in areas of high biodiversity to carry out these types of discoveries would be relatively small compared with the consequences of being surprised again by previously unknown viruses. This type of technology could pay for itself once established because it will serve other purposes, such as basic research, assay development, surveillance, and clinical diagnostics. Virtually all pandemic threats begin as regional outbreaks, including HIV-1. Using available technology to discover and perform surveillance to identify and immediately act on emerging viruses while they are still regional has obvious benefits.

Conflict of interest: The authors are inventors on patent applications involving vaccines and monoclonal antibodies for COVID-19 and other viral diseases.

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While there are more than 100 viral families described, only 25 viral families are known to infect humans. Within those 25 families, there are about 120 known viruses that pose a potential risk (2). There are licensed vaccines for viruses within 13 of those families, but there are large gaps in our knowledge and no vaccines or other countermeasures on the shelf for most of these pathogens. Using new technologies such as structural biology to define the atomic-level details of surface proteins likely to be vaccine targets and enzymes that are relevant antiviral targets, understanding cell tropism and receptor requirements, determining replication mechanisms and capacity for antigenic diversity, and establishing animal models, reagents such as recombinant proteins and monoclonal antibodies, and diagnostic assays would support the development of vaccines and therapeutics for future threats.

Organizing the work based on prototype viral pathogens

Since virus families and genera are organized based on shared functional and structural properties, vaccine solutions within viral families and genera may also be similar. This makes the possibility of using an in-depth knowledge of prototype viral pathogens within each family or genus to inform the development of vaccines and therapeutics for other closely related family members (2). With sufficient

basic knowledge and reagents, a sustained effort could achieve candidate vaccines and therapeutics for representative pathogens within each category through phase 1 clinical evaluation, and countermeasures for the other known threats could be developed through animal model testing. This is a large but tractable effort that could be accomplished over the next ten to twenty years, given a relatively modest investment in facilities and resources. This type of work has been done for coronaviruses since the MERS-CoV outbreak in 2013 and has provided the basic information needed to make a relatively rapid response to the current COVID-19 pandemic (3).

If we have products available ahead of time or that can be rapidly made, there needs to be a global infrastructure through which they can be deployed. Establishing and maintaining prospective cohorts around the world for surveillance could also serve as part of a clinical trials network for rapidly testing medical countermeasures. This network may need to be accompanied by reenvisioned processes to accelerate regulatory pathways ensuring that safe and ethical evaluation of new products can be conducted rapidly in the setting of a crisis. These processes could involve regional or global consortia of regulatory authorities sharing best practices and expertise and maintaining preestablished protocols to facilitate rapid implementation of studies.

As we ascend from the COVID-19 crisis and look toward an uncertain future, our hope is that application of currently available technology in a sustained effort will eclipse short-term planning and provide avenues to successfully launch global infrastructure building and studies of prototype pathogens to achieve better pandemic preparedness and response.

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