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INVITED PERSPECTIVE

Pandemic Preparedness and Response: Lessons From COVID-19

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The global experience with COVID-19 holds important lessons for preparing for, and responding to, future emergences of pathogens with pandemic potential.

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, coronavirus disease 2019 (COVID-19), are responsible for the most catastrophic acute infectious disease outbreak that the United States (US) and the entire world have experienced since the historic influenza pandemic of 1918–1919. More than 1.1 million COVID-19 deaths have been reported in the US, and nearly 7 million globally [1]; the latter figure is likely a vast underestimate [2]. Given the enormous impact of this pandemic on virtually every aspect of global society, it is critical that we reflect on the lessons we have learned (or should have learned) over the past 3 years. Although dozens of lessons could be addressed [3], we have chosen 10 that are noteworthy (Table 1).

The first lesson is inherent to any newly emergent infectious pathogen with pandemic potential: expect the unexpected. Within the broad category of "the unexpected," the COVID-19 pandemic has been unprecedented for the evolution and spread of multiple, successive viral variants with progressively greater capacity for evading immunity induced by vaccines, prior infection, or monoclonal antibodies directed against specific viral epitopes [4]. Another unexpected and unprecedented element of the outbreak is that up to 60% of SARS-CoV-2 transmissions may occur from a person who is asymptomatic [5], which has negated the syndromic approach to contact tracing that has proven effective during many previous infectious disease outbreaks.

The second lesson is the importance of acting early, rapidly, and aggressively in implementing public health interventions and countermeasure development. When dealing with a highly transmissible infection, especially one spread frequently by asymptomatic individuals, the epidemic curve of severe cases or death at any given time reflects transmission that occurred weeks ago. What is happening now will not be evident in morbidity and mortality data until weeks from now. What starts off as an apparent linear increase in cases soon becomes exponential. Playing "catch up" in a pandemic is bound to be a losing proposition.

The third lesson is that global information-sharing and collaborations are essential for a successful response to a pandemic [6]. Sharing of viral isolates, viral genomic data, research reagents, variant surveillance data, clinical samples, and real-world clinical data are essential to optimally utilize the global expertise that exists and is often the gateway to productive international collaborations. During the height of the COVID-19 pandemic, considerable advantages were realized by information made available to US investigators and public health officials by our British, Israeli, and South African colleagues, among others.

A fourth lesson is the importance of leveraging already existing capabilities such as the extensive domestic and international network of clinical trial infrastructure that had been put in place and

Table 1. Ten Lessons From COVID-19 for Pandemic Preparedness

1. Expect the unexpected.
2. Early, rapid, and aggressive action is critical in implementing public health interventions and countermeasure development.
3. Global information sharing and collaborations are essential for a successful response to a pandemic.
4. Already existing infrastructure should be leveraged for the rapid and effective performance of clinical trials.
5. Years of investment in basic and clinical research are critical for the rapid development of effective countermeasures.
6. The prototype pathogen approach to pandemic preparedness and response should be implemented.
7. Attention must be paid to perturbations of the animal–human interface.
8. Long-standing systemic health and social inequities that drive pandemic-related disparities must be addressed.
9. Misinformation and disinformation are the enemy of public health and pandemic control.
10. Emerging infections are forever.

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fine-tuned over decades for the conduct of clinical trials for human immunodeficiency virus (HIV) therapeutics, prevention, and vaccines [7]. Well-established clinical research networks including the HIV Prevention Trials Network, the HIV Vaccine Trials Network, the AIDS Clinical Trials Group, and the Infectious Diseases Clinical Research Consortium were united to form the COVID-19 Prevention Network [8]. Thousands of volunteers passed through this consolidated network in clinical trials that demonstrated the safety and high degree of efficacy of several COVID-19 vaccine candidates.

The fifth, and arguably most important, lesson from the COVID-19 pandemic is that sustained investments in basic and clinical research are critical for the rapid development of effective countermeasures essential for an optimal pandemic response [9]. The most cogent example relates to decades of investment in basic research that led to the groundbreaking messenger RNA (mRNA) vaccine platform [10, 11]. In parallel, many years were devoted by multiple groups to perfecting structure-based immunogen design for an (as-yet unsuccessful) HIV vaccine [12], respiratory syncytial virus (RSV) vaccines (in late-stage clinical development) [13], and investigational Middle East respiratory syndrome (MERS) vaccines [14]. This structure-based approach to SARS-CoV-2 immunogen design led to the mutationally stabilized and ultimately highly effective S-2P immunogen employed in the most widely used COVID-19 vaccines [15]. For COVID-19 mRNA vaccines, the timeline from the identification of a pathogen to the development of a safe and effective vaccine was the shortest in the history of vaccinology (Figure 1) [11]. On 10 January 2020, the genomic sequence of SARS-CoV-2 was posted to a public database [16]. Within 5 days, the development of the Moderna COVID-19 vaccine began (the Pfizer product was on a similar timeline). Within 65 days a phase 1 trial of the vaccine was initiated; within 139 days a phase 2 clinical trial was begun; and within 198 days a phase 3 trial began. An interim analysis of the data from the clinical trials found evidence of preliminary efficacy at day 311, and at day 325 an Emergency Use Authorization was submitted to the US Food and Drug Administration [11]. Thus, in less than 12 months from the recognition of this new virus, vaccine doses were ready to go into the arms of individuals. This scientific accomplishment, along with the billions of dollars invested by Operation Warp Speed [17] that allowed mass production of vaccine doses prior to the proof of efficacy, led to an unprecedented accomplishment—a safe and highly effective vaccine available in less than 1 year from the identification of a novel and deadly pathogen. This never could have been accomplished without decades of investment in basic and clinical research.

To sustain the basic and clinical research enterprise critical for pandemic preparedness, a commitment to the vitality and renewal of the biomedical workforce is essential. To meet the varied microbial threats that will no doubt emerge, we must train the next cadre of clinicians and scientists in the fields traditionally associated with infectious diseases, such as microbiology, virology, immunology, epidemiology, and public health. Also essential to pandemic preparedness are individuals trained in the physical, chemical, mathematical, and

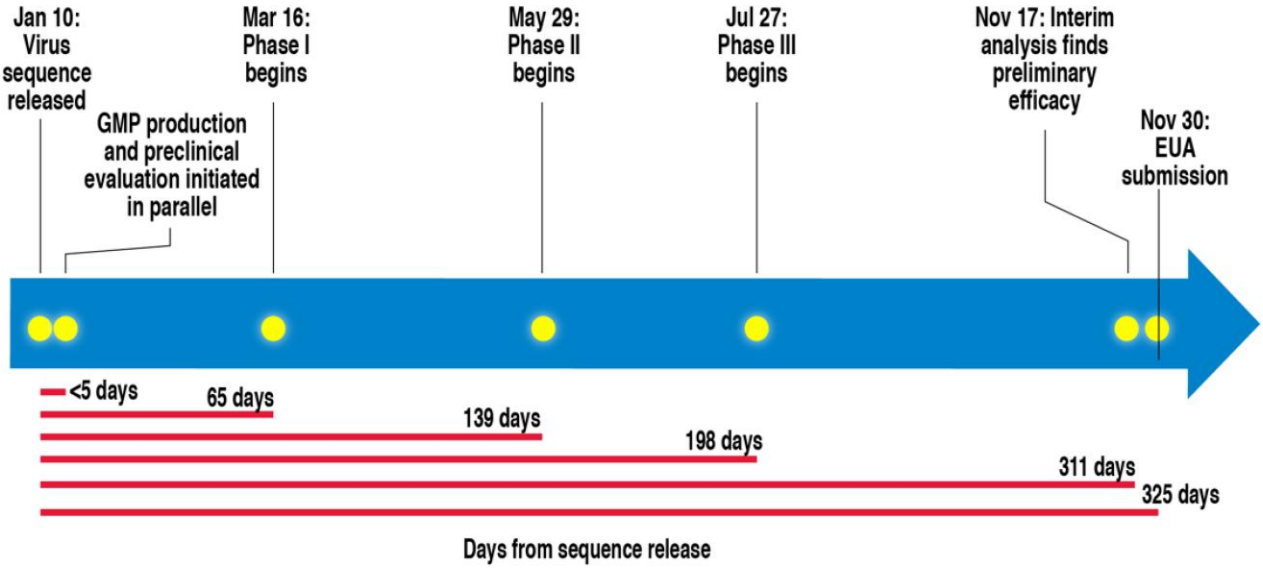

Figure 1. Severe acute respiratory syndrome coronavirus 2 vaccine development: mRNA-1273 (see text for details). Abbreviations: EUA, Emergency Use Authorization; GMP, Good Manufacturing Practice.

computational sciences whose expertise is essential for complex biological challenges, including vaccine development. In addition, a new generation of scientists with expertise in ecology and evolutionary biology is needed to better understand the human–microbe interface, as well as individuals from the veterinary sciences to help illuminate the flow of microbes between animals and humans. We also need skilled individuals in social science disciplines such as anthropology, human geography, and sociology.

The sixth lesson is the utility of the prototype pathogen approach to pandemic preparedness and response. This strategy involves selecting families of viruses with a high potential of being the source of a pandemic outbreak. Such families include Coronaviridae (SARS-CoV-1, MERS, SARS-CoV-2), Orthomyxoviridae (influenza), and Paramyxoviridae (Nipah, RSV), among others [18–20]. The goal is to intensively study a prototype virus in each family in anticipation of the emergence of a novel and potentially pandemic pathogen from within that family. Prior experience with a prototype virus within a given family of viruses regarding basic virology, diagnostic assays, animal models, antigenic targets, optimal vaccine platforms, and potential immune correlates of protection would be informative in the event of the emergence of a potentially pandemic virus within that family. During the COVID-19 pandemic, our prior experience with SARS-CoV-1 and MERS greatly informed and facilitated our response to SARS-CoV-2 [11]. We fully expect that baseline studies of prototype pathogens in the "higher risk" families of viruses will prove extremely useful in allowing a rapid and effective response to the emergence of pathogens of pandemic potential in any of the viral families in question.

The seventh lesson is the importance of attention to perturbations of the animal-human interface [21]. More than 75% of newly emerging human pathogens are zoonotic, having jumped from an animal reservoir to humans. Examples include HIV, influenza, Ebola, SARS, MERS, Nipah, and many others. COVID-19 has taught us again that we must work harder to reduce the risk of pathogen spillover from animals to humans with approaches such as expanding pathogen surveillance at interfaces between humans, domestic animals, and wildlife; strictly limiting the clearing and degradation of tropical and subtropical forests; improving the health and economic security of communities living in emerging infectious disease hotspots; enhancing biosecurity in animal husbandry; and shutting down or strictly regulating wildlife markets and trade [22].

The eighth lesson is that longstanding systemic health and social inequities drive pandemic-related disparities, and these must be addressed [23]. COVID-19 has shed a bright light on how the social determinants of health lead to disparities in incidence and severity of disease. Economic disparities of minority populations such as African Americans and Hispanics result in an overrepresentation in occupations in essential work settings where remote work or physical distancing is difficult or impossible. Underlying conditions such as diabetes, hypertension, obesity, and chronic lung and heart disease, among others, lead to an increased severity of disease once a person is infected. These social determinants of health will not disappear in weeks or months or even years; however, they will never disappear unless we commit now to the process of addressing them.

The ninth lesson comes through loud and clear. Misinformation and disinformation are the enemy of public health and pandemic control [24]. There are many examples of the tragedy of misinformation related to masking, social distancing, vaccine safety, and outright conspiracy theories centered around vaccines that dissuaded individuals from taking advantage of this life-saving countermeasure, leading to the well-documented result of avoidable suffering and death. There is no easy solution to countering this disturbing wave of misinformation and disinformation except for all of us to continue to articulate science- and evidence-based information as proactively as those who spread the opposite.

The tenth lesson is that emerging infections will be with us forever. They always have occurred throughout history; in our lifetime we have experienced many infectious disease emergences, and they surely will occur again in the future [25]. The emergence of new infections may be impossible to prevent; however, stopping their evolution into pandemics is within our control if proper pandemic preparedness and response are implemented.

The entire world has experienced unimaginable suffering over the past 3 years with COVID-19. It is critical that we commit ourselves to ensuring that a pandemic of this magnitude will never happen again. Hopefully, a consideration of these 10 lessons will help us—and those who follow us—to achieve that goal.

Notes

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