Annals of Internal Medicine

SPECIAL ARTICLE

What Recent History Has Taught Us About Responding to Emerging Infectious Disease Threats

Catharine I. Paules, MD; Robert W. Eisinger, PhD; Hilary D. Marston, MD, MPH; and Anthony S. Fauci, MD

Presidential administrations face any number of unexpected crises during their tenure, and global pandemics are among the most challenging. As of January 2017, one of the authors had served under 5 presidents as the director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. During each administration, the government faced unexpected pandemics, ranging from the HIV/AIDS pandemic, which began during the Reagan administration, to the recent Zika outbreak in the Americas, which started during the Obama administration. These experiences underscored the need to optimize preparation for and response to these threats whenever and wherever they emerge. This article recounts selected outbreaks occurring during this period and highlights lessons that were learned that can be applied to the infectious disease threats that will inevitably be faced in the current presidential administration and beyond.

Ann Intern Med. 2017;167:805-811. doi:10.7326/M17-2496 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 14 November 2017.

In mid-January 2017, before the U.S. presidential inauguration, the outgoing Obama administration convened a meeting with most of the cabinet nominees of the incoming administration of President-elect Donald Trump to brief them on the types of unanticipated emergencies they might face (1). In addition to terror attacks, cyberattacks, and natural disasters, outbreaks of infectious diseases were presented as a likely threat. One of us (Anthony S. Fauci) attended that meeting along with other members of the Department of Health and Human Services to discuss emerging infectious diseases. The meeting prompted us to reflect on infectious disease challenges that have arisen during the 5 administrations under which Dr. Fauci has served as director of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) since his appointment in 1984. During this period, each administration was confronted with the need to manage ongoing or established infectious diseases as well as new and reemerging infectious disease threats. This review highlights selected infectious disease outbreaks occurring during this period that are especially memorable and have helped to shape and refine the role of the NIAID's research and public health response to such threats. Because current and as-yet unknown infectious diseases will continue to challenge us, these experiences may also serve as lessons that can be applied during the inevitable public health crises to come.

Infectious diseases, as both a discipline and a research field, were generally perceived as rapidly losing prominence among the key components of public health activity when Ronald Reagan assumed the Presidency of the United States in 1981. Many agreed with Nobel Prize winner and eminent virologist Sir F. Macfarlane Burnet and his colleague Dr. David O. White, who had written a decade earlier that "to write about infectious disease is almost to write of something that has passed into history . . . the most likely forecast about the future of infectious disease is that it will be very dull" (2). To make matters worse for the perception of the field, Dr. Robert G. Petersdorf, an iconic figure in the field of infectious diseases and an important mentor to Dr. Fauci, famously wrote in 1978, in reference to the number of fellows scheduled to take the infectious diseases certifying examination given by the American Board of Internal Medicine, "Even with my great personal loyalties to infectious diseases, I cannot conceive a need for 309 more infectious-disease experts unless they spend their time culturing each other" (3). However, 3 years later, an event occurred that led to the stark realization of the real and potential emergence and reemergence of globally important infectious diseases, heralding a trend that would impact and influence each of the 5 administrations under which Dr. Fauci served.

Less than 6 months into the first year of the 2-term Reagan administration (1981–1989), a puzzling cluster of Kaposi sarcoma and *Pneumocystis* pneumonia among young, previously healthy men who had sex with men in New York City and California was reported by the U.S. Centers for Disease Control (CDC; now the Centers for Disease Control and Prevention) (4, 5). These unusual cases were first believed to be a curiosity limited to a small, marginalized segment of the U.S. population. However, in an *Annals of Internal Medicine* article written in 1981 and published in 1982 (6), Dr. Fauci opined that "because we do not know the cause of this syndrome, any assumption that the syndrome will remain restricted to a particular segment of our society is truly an assumption without scientific basis." This admonition, together with similar warnings from the CDC and other health authorities, presaged a pandemic of unfathomable magnitude. Currently, the Joint United Nations Programme on HIV/AIDS estimates that 37 million persons are living with HIV infection globally, and approximately 35 million have died of AIDS-related illnesses since the start of the epidemic (7).

The Reagan administration, particularly during its first term, was strongly criticized for failing to utilize its bully pulpit to galvanize efforts against this emerging threat (8). Although many infectious disease outbreaks begin dramatically and generate considerable public attention, the insidious emergence of HIV/AIDS and the

lack of due attention by policymakers illustrate how some outbreaks that start subtly can grow to global proportions if they are not aggressively addressed early on.

The NIH began building an HIV/AIDS research program from the ground up. Upon Dr. Fauci assuming the directorship of the NIAID in 1984, the institute immediately scaled up its research effort after the co-discovery of HIV as the cause of AIDS by Luc Montagnier, Françoise Barré-Sinoussi, and their team at the Institut Pasteur in Paris, France (9), and Robert Gallo and his team (10) in the NIH Intramural Research Program. Of note, a distinct AIDS program to fund extramural researchers was established to bring investigators into a field that desperately needed a rapid influx of scientists from different disciplines.

During its second term, the leadership of the Reagan administration took a more active public role in response to the AIDS outbreak with the 1986 issuance of the "Surgeon General's Report on Acquired Immune Deficiency Syndrome" (11) and the subsequent establishment of the first AIDS Commission, announced when Reagan visited the NIH on 23 July 1987. Despite this increased effort, these actions were regarded by activists as inadequate for the challenge at hand.

Simultaneously, in anticipation of his running for president in 1988, then–Vice President George H.W. Bush began taking an interest in the emerging HIV/AIDS pandemic. He visited the NIH Clinical Center on 8 April 1987 and met with HIV-infected patients and NIH researchers to learn firsthand about HIV/AIDS (12). Building on the interest he showed while vice president, upon becoming president in 1989, he took a much different approach from his predecessor in recognizing and responding to the growing HIV/AIDS epidemic. At that time, only a few years after HIV had been identified, patients generally presented to health care providers with advanced disease and a life expectancy ranging from a few months to 1 or 2 years (13, 14). Given the rapidly mounting death toll, federal funding for HIV/AIDS research was increased to more than $1 billion by the end of the George H.W. Bush administration.

Over the coming years, this significant investment in science led to extraordinary advances in all aspects of HIV/AIDS research, from viral pathogenesis to immunopathogenesis, laying the groundwork for the development of targeted antiviral therapy. Such research ultimately resulted in the introduction of combinations of antiretroviral drugs that transformed HIV/AIDS from a nearly universally fatal disease to a manageable illness in areas of the world where such drugs are available. The accelerated U.S. government response to the HIV/AIDS epidemic, which had its beginnings in the George H.W. Bush administration, demonstrated the importance of investing resources in fundamental scientific research, including research infrastructure. It also put into sharp focus the critical need to promote direct communication with affected communities and to garner the support of political leaders and policymakers in responding to public health crises. The evolution of this approach was slow at first, and the unrelenting pressure of HIV/AIDS activists played a critical role in accelerating the process (15). It soon became clear that there were distinct advantages of early participation of involved communities in the government response to the HIV/AIDS pandemic in the areas of public health and biomedical research.

The Clinton administration (1993–2001) was confronted with both the ongoing management of the HIV/AIDS pandemic and 2 new infectious disease challenges: the emergence of H5N1 avian influenza and the reemergence of West Nile virus in the Americas. With regard to the HIV/AIDS pandemic, the administration's sustained and accelerated investment in NIH research and strong collaboration with pharmaceutical companies continued to fuel scientific discoveries, particularly in the arena of treatment. This led to advances in combination antiretroviral therapy (ART) that have transformed the lives of HIV-infected persons. The 1- to 2-year median survival seen in the early years of the pandemic increased dramatically and set the stage for what we see today: an almost normal life expectancy for persons who are diagnosed early and maintain viral suppression through combination ART (16). To complement ongoing treatment research, attention turned to the importance of developing an HIV vaccine, and the NIH refocused its HIV vaccine efforts on basic immunology to accelerate the development of potential candidates. To address this key goal, and with strong encouragement from the NIH, in 1997, President Clinton announced the establishment of an NIH Vaccine Research Center (VRC). This facility, now part of the NIAID, has made pivotal contributions to HIV/AIDS research while also evolving into a critical component of the NIAID's response to other chronic and emerging infectious diseases.

In 1997, during its second term, the Clinton administration was faced with the emergence of H5N1 avian influenza in Hong Kong (17, 18). These infections were highly concerning given that international travel had increased dramatically by the turn of the millennium, underscoring the reality that we live in a global community. The NIAID followed this outbreak carefully and noted that mortality in persons infected directly through contact with birds was a striking 33% (18). Fortunately, the virus did not achieve the capacity to spread efficiently from person to person, and aggressive culling of poultry by the Hong Kong health authorities resulted in a temporary end to the outbreak. However, this event led to close surveillance for and attention to "prepandemic" viruses that threaten to evolve into pandemic influenza viruses. However, the H5N1 prepandemic influenza virus would capture our attention again.

In addition to the emergence of H5N1 avian influenza, the Clinton administration was faced with the reemergence of West Nile virus, a well-known global infectious disease that had never been observed in the Americas. West Nile virus is a classic example of an old infection that reemerges in a new geographic location. This flavivirus, previously endemic to Africa and the

Middle East, first appeared in the Americas in 1999, causing 59 cases of encephalitis and 7 deaths in New York (19). The virus spread rapidly and has since become endemic in the continental United States. In response to this outbreak, the NIAID VRC developed a vaccine against West Nile virus and completed a phase 1 clinical trial (20). Unfortunately, the vaccine was not developed further because of the lack of an industry partner. However, it showed the utility of a new vaccine platform (DNA) that would undergo advanced development in a subsequent flavivirus outbreak.

The George W. Bush administration (2001–2009) was faced almost immediately with 2 unprecedented domestic public health emergencies. The devastating terrorist attacks of 11 September 2001 were followed within days by detection of anthrax spores in letters to 2 U.S. senators and certain members of the press, likely the result of a deliberate release in the postal system. Twenty-two persons were known to have been infected with anthrax, 5 of whom died (21). With a substantial infusion of new funding, these attacks spurred the launch of a massive endeavor focused on public health preparedness for bioterrorist threats, particularly but not exclusively from infectious diseases. At the time of the anthrax attacks, the NIAID had a modest basic science research program on potential agents of bioterrorism (22). In response to the attacks, the institute issued a series of initiatives and used newly obligated resources to greatly expand its research portfolio. In 2002, the NIAID published its "Strategic Plan for Biodefense Research" (23) and the "NIAID Biodefense Research Agenda for CDC Category A Agents" (24). The reinvigorated research effort focused heavily on countermeasure development and led to several key achievements, including the development of vaccine candidates against smallpox and *Clostridium botulinum*, antivirals for smallpox, antitoxins for anthrax and botulinum, and the first clinical Ebola vaccine trials. At that time, Ebola was among a group of hemorrhagic fever viruses categorized as CDC category A agents and known to have been stockpiled by the former Soviet Union (25). The importance of the basic and translational research on Ebola conducted during the George W. Bush administration was not fully appreciated until later.

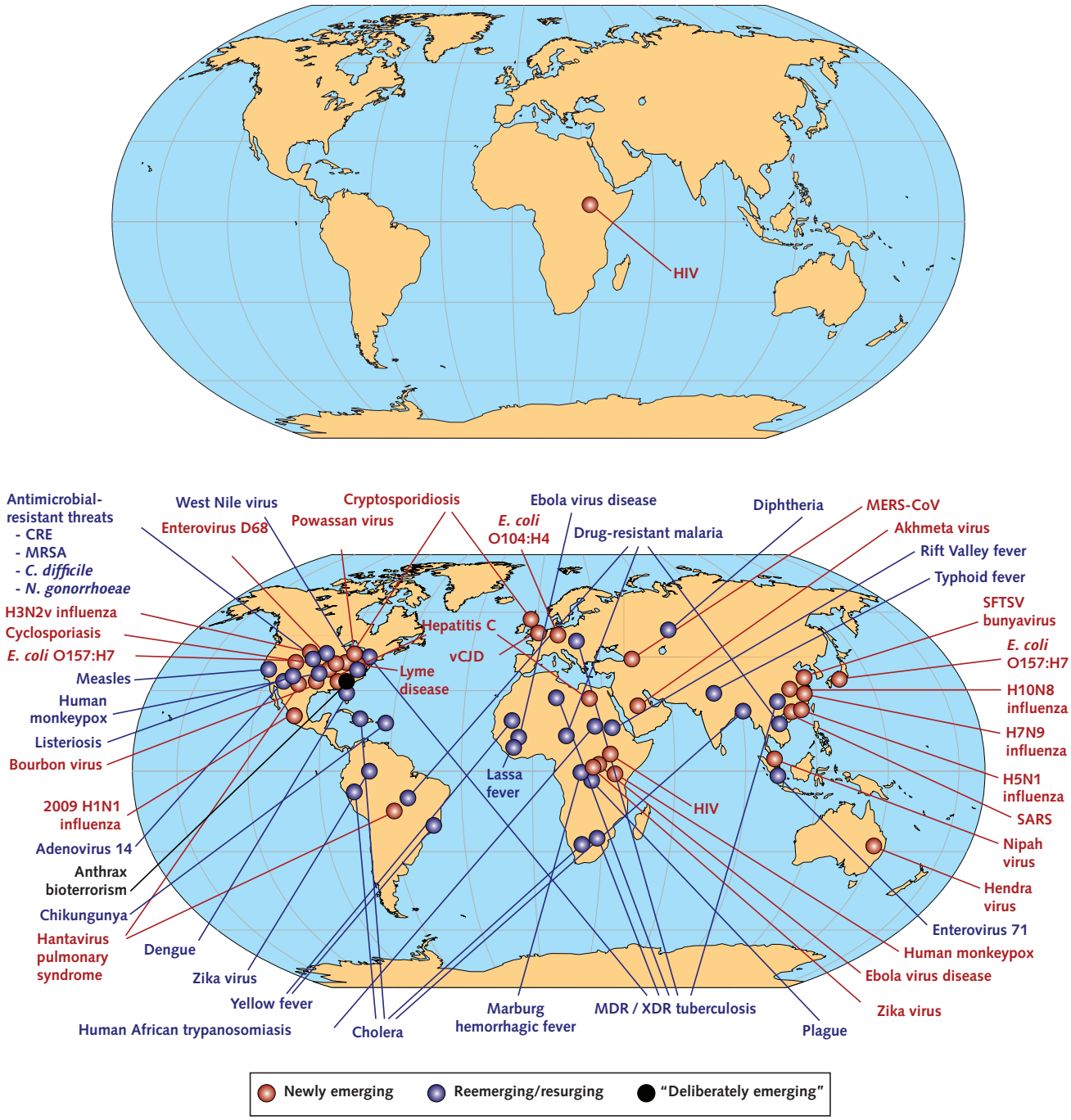
Although the anthrax attacks generated considerable public fear and even panic about the use of biological agents in acts of bioterrorism, NIAID leadership and many scientific and public health colleagues believed that the natural emergence of a virulent pathogen was an even greater threat (26). Nowhere was this more clearly illustrated than during the next few years of the George W. Bush administration, when severe acute respiratory syndrome emerged in 2002 and H5N1 influenza reemerged in 2003.

In late 2002, several cases of an unexplained severe atypical pneumonia were reported in the Guangdong province of China, and by February 2003, the number of cases totaled more than 300, with at least 5 deaths (27). Shortly thereafter, this disease, by then termed severe acute respiratory syndrome (SARS), resulted in worldwide panic as it spread globally via air travel, with sporadic cases in some countries and more sustained clusters of transmission in others. The SARS pandemic, which was subsequently found to be caused by a novel coronavirus, resulted in 8096 cases and 774 deaths before the outbreak ended (28) and had a substantial negative effect on national and global economies. The outbreak was successfully controlled with classic public health measures, including early case identification, patient isolation, and use of personal protective equipment by health care workers, even before specific countermeasures were developed. The NIAID played a critical role in the research response to SARS, developing preclinical vaccine candidates in less than a year by using several novel technologies (29–31). Given the resolution of the SARS pandemic, the leading vaccine candidates were not commercially developed; however, they are serving as templates for vaccine approaches to other coronaviruses. Moreover, this rapid response set the pace for our research response to future infectious disease threats.

On the heels of the SARS outbreak, H5N1 influenza reemerged in East and Southeast Asia in 2003, causing infections in both birds and humans (18). Person-to-person transmission was suspected in several case clusters, and although it was inefficient, it caused global concern that the virus might mutate to adapt itself to humans and precipitate the next worldwide influenza pandemic (32). In response, an all-government approach to pandemic preparedness was developed, culminating in the publication of a "National Strategy for Pandemic Influenza" (33) and related implementation plans. Congress, responding to the Bush administration's request, provided billions of dollars in emergency spending to combat the threat of a global influenza pandemic. The NIAID, together with its grantees and contractors, played a key role in testing vaccine candidates against H5N1 influenza, some of which were later manufactured and placed in the Strategic National Stockpile.

Contemporaneous to these emerging infectious disease threats, the global HIV/AIDS epidemic continued to expand, fueled in large part by an explosive increase in infections in sub-Saharan Africa. In 2003, approximately one third of the population of several sub-Saharan African countries was infected with HIV, and more than 20 million persons had died of AIDS (34). Despite the availability of safe and effective therapies to treat HIV infection, only a fraction of infected persons were receiving treatment. In response to this crisis, President George W. Bush launched a $15 billion, 5-year program, named the President's Emergency Plan for AIDS Relief (PEPFAR), in 2003. This program had ambitious goals, including preventing 7 million new HIV infections; treating 2 million HIV-infected persons; and providing care, such as basic medical services, education, and social support, for 10 million HIV-infected persons and AIDS orphans (35). PEPFAR, which has received continuous funding, is the largest global health initiative for a single infectious disease that has ever been implemented by any country.

Figure. Global examples of emerging and reemerging infectious diseases.



C. difficile = *Clostridium difficile*; CRE = carbapenem-resistant Enterobacteriaceae; *E. coli* = *Escherichia coli*; H3N2v = H3N2 variant; MDR = multidrug-resistant; MERS-CoV = Middle East respiratory syndrome coronavirus; MRSA = methicillin-resistant *Staphylococcus aureus*; *N. gonorrhoeae* = *Neisseria gonorrhoeae*; SARS = severe acute respiratory syndrome; SFTSV = severe fever with thrombocytopenia syndrome virus; vCJD = variant Creutzfeldt–Jakob disease; XDR = extensively drug-resistant. **Top.** Map of the world drawn in the early 1980s and indicating the predominant newly emerging infectious disease at that time (HIV). **Bottom.** Accumulation of some newly emerging and reemerging infectious diseases since the early 1980s and several that were encountered before then. Some infectious disease outbreaks have had major global health impact, whereas others have appeared as curiosities, with little public health impact. Adapted from reference 50.

As of March 2017, PEPFAR had treated 12.3 million HIV-infected men, women, and children with ART; funded 12.5 million voluntary medical male circumcisions in eastern and southern African nations to reduce the risk for HIV transmission; and provided care for more than 6.2 million orphans and vulnerable children to decrease the physical, psychological, and financial impact of HIV on this high-risk group (36, 37).

Similar to the George W. Bush administration, the Obama administration (2009–2017) experienced the first of several unanticipated infectious disease threats in the early months of its first term. The H1N1 influenza pandemic, the first influenza pandemic of the 21st century, began in April 2009, just months after the inauguration. Because seasonal influenza vaccines offered little or no protection against this newly emerged virus, Congress acted quickly to give the Department of Health and Human Services significant additional resources in anticipation of a second phase of the outbreak in the fall and winter of 2009. Vaccine development was deemed to be the highest priority, and in early August 2009, as soon as an experimental vaccine was available, the NIAID began rapidly enrolling volunteers into a clinical trial conducted by its Vaccine and Treatment Evaluation Units network. However, despite intense efforts to rapidly develop and test the vaccine, trial results and vaccine supplies were not available until the late fall and early winter, after the outbreak had peaked (38).

This experience served as a striking reminder of the inadequacy of our pandemic preparedness capabilities and underscored the need, now being actively pursued, to develop platform technologies that can be applied rapidly to develop vaccines for evolving outbreaks. As in the example of influenza, history has shown that we will be continually threatened by prepandemic and pandemic viruses and that it is extremely difficult to "chase" an emerging virus. The need to develop a more broadly protective "universal" influenza vaccine that is effective against seasonal as well as novel influenza viruses has become clear, and the NIAID has made the marshaling of talent from multiple scientific disciplines to actively pursue the development of such a vaccine a top priority.

Infectious disease outbreaks continued to dominate the global health arena throughout the Obama administration. The 2009 H1N1 influenza pandemic was followed in quick succession by outbreaks of chikungunya in the Caribbean in 2013; Ebola in West Africa in 2014; and, finally, Zika in the southern regions of the Americas in 2015. Chikungunya virus, an alphavirus that had previously caused outbreaks in parts of Africa, Asia, Europe, and the Pacific islands, was first noted in the Caribbean in 2013 and subsequently spread rapidly throughout the Caribbean and Central and South America. It has since caused disease in approximately 2 million persons in the region, with outbreaks ongoing in many countries (39). The NIAID VRC responded quickly to this threat by developing a novel chikungunya virus–like particle vaccine (40) that is currently in a phase 2 study. This rapid response is a dramatic example of the power of utilizing preexisting platform technologies to expedite vaccine development during an outbreak.

The reemergence of chikungunya virus was followed by the devastating Ebola crisis in West Africa, which peaked in 2014. This outbreak was the result of a "perfect storm" in which a lethal disease spread rampantly in the crowded urban centers of countries that lacked public health infrastructure. By the end of the outbreak, Guinea, Liberia, and Sierra Leone reported more than 28 000 cases of Ebola, with 11 310 deaths (41). The American public reacted to Ebola with a level of fear and panic that was disproportionate to the actual risk to the U.S. population. Although several Ebola-infected persons were treated in the United States, all but 2 of the cases were acquired during health care provision in countries affected by the epidemic. In addition, most U.S. cases were treated in specialized isolation units by highly trained personnel and posed no danger to the general public. The NIH Clinical Center Special Clinical Studies Unit was one such facility, successfully treating 2 Ebola-infected persons.

Table. Optimal Response to Emerging Infectious Disease Outbreaks: Lessons Learned

Global surveillance to detect outbreaks early
Transparency and communication in response to outbreaks
Incorporation of infrastructure and capacity building domestically and internationally in outbreak responses
Conduct of basic and clinical research associated with outbreaks in a coordinated and collaborative manner
Involvement of the afflicted communities in policy decisions
Pursuit and perfection of adaptable platform technologies for vaccines, diagnostics, and therapeutics
Importance of flexible funding mechanisms

In response to the Ebola crisis, the NIH, at the request of the Liberian Ministry of Health, launched a unique collaboration, the Partnership for Research on Ebola Virus in Liberia (PREVAIL), to better understand the natural history of Ebola and to build a clinical research infrastructure to evaluate candidate vaccines and therapeutics. PREVAIL-sponsored studies of several vaccine candidates (42) and the monoclonal antibody therapy ZMapp (Mapp Biopharmaceutical) (43) showed that even during an outbreak, rigorous clinical trials are both feasible and welcomed by affected populations. These trials offered important information to guide responses to future Ebola outbreaks. However, in the end, infrastructure development; close collaboration with the host countries; and the implementation of classic public health measures, such as safe burial practices and meticulous contact tracing, brought this historic epidemic to a halt.

The arrival of Zika virus in the Americas was the final major infectious disease threat confronted during the Obama administration. Zika virus, an obscure flavivirus believed to have limited clinical significance, was detected in Brazil in 2015 and was thrust into the public eye when it was linked to an upsurge in microcephaly in Brazil (44) and other countries. Zika virus has since spread throughout the southern regions of the Americas, causing widespread disease. Puerto Rico and other U.S. territories were hit especially hard by locally transmitted infections. In addition, thousands of travel-related cases were seen in the continental United States, together with more than 200 locally transmitted cases in Florida and a small cluster of infections in Texas (45). In addition to microcephaly, Zika virus has been linked to several other congenital abnormalities

(46), as well as serious clinical manifestations in adults, such as Guillain–Barré syndrome (47) and encephalitis (48). In response to this outbreak, the NIH rapidly launched a comprehensive research program to better understand the natural history and pathogenesis of Zika and develop effective countermeasures, such as vaccines. One NIH vaccine candidate, the VRC's investigational DNA vaccine, was created by utilizing a platform initially developed for West Nile virus. The time frame from obtaining the sequence of Zika virus to the initiation of a phase 1 clinical trial in humans was an extraordinarily short 3 to 4 months (49), and the vaccine candidate is currently in a phase 2/2b clinical trial, again demonstrating the importance of perfecting platform technologies to permit rapid vaccine development during an outbreak.

In 1984, when Dr. Fauci became director of the NIAID, he drew a map of the world for presentation at a congressional hearing that showed a single notable emerging infectious disease threat: HIV (**Figure**, *top*). Since then, he has continually updated the map, now showing the emergence of numerous infectious disease threats to illustrate the experiences of the past 33 years as well as highlighting certain infections that had emerged before HIV (**Figure**, *bottom*).

The current administration will undoubtedly be challenged by unanticipated infectious disease outbreaks. Leadership at the NIAID has learned many valuable lessons through experiences during the prior administrations with regard to optimal responses to such outbreaks (**Table**). It is critical to apply these lessons to the infectious disease threats that we will inevitably face in the current administration and beyond. Contrary to the predictions of infectious disease leaders of the mid–20th century, such as Sir F. Macfarlane Burnet (2) and Robert G. Petersdorf (3), we have not seen the end of the era of infectious diseases. We are certain that were these men alive today, both would agree emphatically and would encourage us to remain vigilant and prepared (50).

From Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Note: This article is based on a lecture given by Anthony S. Fauci, MD, on 30 March 2017 in San Diego, California, at the Internal Medicine Meeting 2017 of the American College of Physicians.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-2496.

Requests for Single Reprints: Catharine I. Paules, MD, Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Building 31, Suite 7A03, Bethesda, MD 20892; e-mail, catharine.paules@nih.gov.

Current author addresses and author contributions are available at Annals.org.

References

1. **Fabian J.** White House holds disaster-response exercise with Trump officials. The Hill. 13 January 2017.
2. **Burnet M, White DO.** Natural History of Infectious Disease. 4th ed. Cambridge, UK: Cambridge Univ Pr; 1972.
3. **Petersdorf RG.** The doctors' dilemma. N Engl J Med. 1978;299:628-34. [PMID: 683236]
4. **Centers for Disease Control (CDC).** *Pneumocystis* pneumonia–Los Angeles. MMWR Morb Mortal Wkly Rep. 1981;30:250-2. [PMID: 6265753]
5. **Centers for Disease Control (CDC).** Kaposi's sarcoma and *Pneumocystis* pneumonia among homosexual men–New York City and California. MMWR Morb Mortal Wkly Rep. 1981;30:305-8. [PMID: 6789108]
6. **Fauci AS.** The syndrome of Kaposi's sarcoma and opportunistic infections: an epidemiologically restricted disorder of immunoregulation [Editorial]. Ann Intern Med. 1982;96:777-9. [PMID: 7091942] doi:10.7326/0003-4819-96-6-777
7. **UNAIDS.** Fact Sheet: Latest Global and Regional Statistics on the Status of the AIDS Epidemic. 20 July 2017. Accessed at www.unaids.org/en/resources/documents/2017/UNAIDS_FactSheet on 9 August 2017.
8. **Scheer R.** Early indifference to AIDS is blamed for its spread. Los Angeles Times. 29 November 1986.
9. **Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al.** Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983;220:868-71. [PMID: 6189183]
10. **Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, et al.** Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science. 1984;224:500-3. [PMID: 6200936]
11. **U.S. Public Health Service, Office of the Surgeon General.** Surgeon General's Report on Acquired Immune Deficiency Syndrome. Washington, DC: U.S. Public Health Service; 1986.
12. Vice President Bush Visits Clinical Center, Gets AIDS Update from Experts. NIH Record. 1987;39:1-2. Accessed at https://history.nih.gov/nihinownwords/assets/media/pdf/publications/RecordApr21-87.pdf on 13 September 2017.
13. **Hellinger FJ.** The lifetime cost of treating a person with HIV. JAMA. 1993;270:474-8. [PMID: 8320787]
14. **Rothenberg R, Woelfel M, Stoneburner R, Milberg J, Parker R, Truman B.** Survival with the acquired immunodeficiency syndrome. Experience with 5833 cases in New York City. N Engl J Med. 1987;317:1297-302. [PMID: 3500409]
15. **Piot P, Russell S, Larson H.** Good politics, bad politics: the experience of AIDS [Editorial]. Am J Public Health. 2007;97:1934-6. [PMID: 17901417]
16. **Marcus JL, Chao CR, Leyden WA, Xu L, Quesenberry CP Jr, Klein DB, et al.** Narrowing the gap in life expectancy between HIV-infected and HIV-uninfected individuals with access to care. J Acquir Immune Defic Syndr. 2016;73:39-46. [PMID: 27028501] doi:10.1097/QAI.0000000000001014
17. **Subbarao K, Klimov A, Katz J, Regnery H, Lim W, Hall H, et al.** Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. Science. 1998;279:393-6. [PMID: 9430591]
18. **World Health Organization.** H5N1 highly pathogenic avian influenza: timeline of major events. 4 December 2014. Accessed at www.who.int/influenza/human_animal_interface/H5N1_avian_influenza_update20141204.pdf on 22 August 2017.
19. **Nash D, Mostashari F, Fine A, Miller J, O'Leary D, Murray K, et al; 1999 West Nile Outbreak Response Working Group.** The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med. 2001;344:1807-14. [PMID: 11407341]

20. **Ledgerwood JE, Pierson TC, Hubka SA, Desai N, Rucker S, Gordon IJ, et al; VRC 303 Study Team.** A West Nile virus DNA vaccine utilizing a modified promoter induces neutralizing antibody in younger and older healthy adults in a phase I clinical trial. J Infect Dis. 2011;203:1396-404. [PMID: 21398392] doi:10.1093/infdis/jir054
21. **Centers for Disease Control and Prevention.** Anthrax. The Threat. Updated 1 August 2014. Accessed at www.cdc.gov/anthrax/bioterrorism/threat.html on 9 August 2017.
22. **Lane HC, Montagne JL, Fauci AS.** Bioterrorism: a clear and present danger. Nat Med. 2001;7:1271-3. [PMID: 11726956]
23. **U.S. Department of Health and Human Services; National Institutes of Health; National Institute of Allergy and Infectious Diseases.** NIAID Strategic Plan for Biodefense Research. Washington, DC: U.S. Department of Health and Human Services; 2002.
24. **U.S. Department of Health and Human Services; National Institutes of Health; National Institute of Allergy and Infectious Diseases.** NIAID Biodefense Research Agenda for CDC Category A Agents. Washington, DC: U.S. Department of Health and Human Services; 2002.
25. **Borio L, Inglesby T, Peters CJ, Schmaljohn AL, Hughes JM, Jahrling PB, et al; Working Group on Civilian Biodefense.** Hemorrhagic fever viruses as biological weapons: medical and public health management. JAMA. 2002;287:2391-405. [PMID: 11988060]
26. **Hirschberg R, La Montagne J, Fauci AS.** Biomedical research—an integral component of national security. N Engl J Med. 2004;350:2119-21. [PMID: 15152055]
27. **Peiris JS, Yuen KY, Osterhaus AD, Stöhr K.** The severe acute respiratory syndrome. N Engl J Med. 2003;349:2431-41. [PMID: 14681510]
28. **World Health Organization.** Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Updated 31 December 2003. Accessed at www.who.int/csr/sars/country/table2004_04_21/en on 9 August 2017.
29. **Bisht H, Roberts A, Vogel L, Bukreyev A, Collins PL, Murphy BR, et al.** Severe acute respiratory syndrome coronavirus spike protein expressed by attenuated vaccinia virus protectively immunizes mice. Proc Natl Acad Sci U S A. 2004;101:6641-6. [PMID: 15096611]
30. **Yang ZY, Kong WP, Huang Y, Roberts A, Murphy BR, Subbarao K, et al.** A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. Nature. 2004;428:561-4. [PMID: 15024391]
31. **Bukreyev A, Lamirande EW, Buchholz UJ, Vogel LN, Elkins WR, St Claire M, et al.** Mucosal immunisation of African green monkeys (*Cercopithecus aethiops*) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. Lancet. 2004;363:2122-7. [PMID: 15220033]
32. **Ungchusak K, Auewarakul P, Dowell SF, Kitphati R, Auwanit W, Puthavathana P, et al.** Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med. 2005;352:333-40. [PMID: 15668219]
33. **Homeland Security Council.** National Strategy for Pandemic Influenza. Washington, DC: Homeland Security Council; 2005.
34. **Office of the U.S. Global AIDS Coordinator.** PEPFAR 3.0: Controlling the Epidemic: Delivering on the Promise of an AIDS-Free Generation. 2014. Accessed at www.pepfar.gov/documents/organization/234744.pdf on 9 August 2017.
35. **Office of the Press Secretary.** Fact Sheet: The President's Emergency Plan for AIDS Relief. 29 January 2003. Accessed at https://georgewbush-whitehouse.archives.gov/news/releases/2003/01/20030129-1.html on 9 August 2017.
36. **U.S. President's Emergency Plan for AIDS Relief (PEPFAR).** Fact Sheet: PEPFAR Latest Global Results. 2016. Accessed at www.pepfar.gov/documents/organization/264882.pdf on 13 September 2017.
37. **U.S. President's Emergency Plan for AIDS Relief (PEPFAR).** Statement by Ambassador Deborah L. Birx: U.S. Government/PEPFAR's global commitment to HIV/AIDS remains strong [press release]. 20 July 2017. Accessed at www.pepfar.gov/press/releases/2017/272760.htm on 9 August 2017.
38. **Centers for Disease Control and Prevention.** The 2009 H1N1 Pandemic: Summary Highlights, April 2009–April 2010. Updated 16 June 2010. Accessed at www.cdc.gov/h1n1flu/cdcresponse.htm on 24 August 2017.
39. **Centers for Disease Control and Prevention.** Chikungunya Virus. Updated 29 August 2017. Accessed at www.cdc.gov/chikungunya/index.html on 9 August 2017.
40. **Chang LJ, Dowd KA, Mendoza FH, Saunders JG, Sitar S, Plummer SH, et al; VRC 311 Study Team.** Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. Lancet. 2014;384:2046-52. [PMID: 25132507] doi:10.1016/S0140-6736(14)61185-5
41. **World Health Organization.** Ebola virus disease. Updated June 2017. Accessed at www.who.int/mediacentre/factsheets/fs103/en on 9 August 2017.
42. **National Institute of Allergy and Infectious Diseases.** Experimental Ebola vaccines well tolerated, immunogenic in phase 2 study [press release]. 23 February 2016. Accessed at www.niaid.nih.gov/news-events/experimental-ebola-vaccines-well-tolerated-immunogenic-phase-2-study on 2 October 2017.
43. **Davey RT Jr, Dodd L, Proschan MA, Neaton J, Neuhaus Nordwall J, Koopmeiners JS, et al; PREVAIL II Writing Group.** A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med. 2016;375:1448-56. [PMID: 27732819]
44. **Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A, et al; Brazilian Medical Genetics Society–Zika Embryopathy Task Force.** Possible association between Zika virus infection and microcephaly—Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016;65:59-62. [PMID: 26820244] doi:10.15585/mmwr.mm6503e2
45. **Centers for Disease Control and Prevention.** Zika Cases in the United States. Updated 16 August 2017. Accessed at www.cdc.gov/zika/reporting/case-counts.html on 22 August 2017.
46. **Steele RW.** Zika virus: an explosive pandemic and a new TORCH agent. Clin Pediatr (Phila). 2016;55:698-700. [PMID: 27000068] doi:10.1177/0009922816638660
47. **Dos Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, de Oliveira WK, et al.** Zika virus and the Guillain-Barré syndrome—case series from seven countries [Letter]. N Engl J Med. 2016;375:1598-1601. [PMID: 27579558]
48. **da Silva IRF, Frontera JA, Bispo de Filippis AM, Nascimento OJMD; RIO-GBS-ZIKV Research Group.** Neurologic complications associated with the Zika virus in Brazilian adults. JAMA Neurol. 2017. [PMID: 28806453] doi:10.1001/jamaneurol.2017.1703
49. **National Institute of Allergy and Infectious Diseases.** NIH begins testing investigational Zika vaccine in humans [press release]. 3 August 2016. Accessed at www.niaid.nih.gov/news-events/nih-begins-testing-investigational-zika-vaccine-humans on 2 October 2017.
50. **Fauci AS.** Infectious diseases: considerations for the 21st century. Clin Infect Dis. 2001;32:675-85. [PMID: 11229834]

Current Author Addresses: Drs. Paules, Eisinger, Marston, and Fauci: Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Building 31, Suite 7A03, Bethesda, MD 20892.

Author Contributions: Conception and design: C.I. Paules, R.W. Eisinger, A.S. Fauci.
Analysis and interpretation of the data: R.W. Eisinger.
Drafting of the article: C.I. Paules, R.W. Eisinger, H.D. Marston, A.S. Fauci.
Critical revision of the article for important intellectual content: R.W. Eisinger.
Final approval of the article: C.I. Paules, R.W. Eisinger, H.D. Marston, A.S. Fauci.
Administrative, technical, or logistic support: A.S. Fauci.
Collection and assembly of data: R.W. Eisinger.