The 1918 flu, 100 years later

C ombating a disease of unknown cause is a daunting task. One hundred years ago, a pandemic of poorly understood etiology and transmissibility spread worldwide, causing an estimated 50 million deaths. Initially attributed to *Haemophilus influenzae*, it was not until the 1930s that an H1 subtype was identified as the causative strain. Subsequent influenza pandemics in 1957, 1968, and 2009 did not approach levels of morbidity and mortality comparable to those of the 1918 “Spanish flu,” leaving unanswered for almost a century questions regarding the extraordinary virulence and transmissibility of this unique strain. Technological advances made reconstruction of the 1918 virus possible; now, continued research, vaccine development, and preparedness are essential to ensure that such a devastating public health event is not repeated.

Over the past 20 years, studies of individual genes and the fully reconstructed live 1918 virus have identified numerous features that likely contributed to its robustness and rapid global spread. Importantly, this research has often been conducted in tandem with viral isolates from recent human and zoonotic sources, enabling insights from the 1918 virus to inform evaluations of current pandemic risk. As we now know, wild birds are the natural reservoir for influenza A viruses. With extensive antigenic and genetic diversity inherent among influenza virus surface proteins, a strain to which humans are immunologically naïve could jump the species barrier at any time. A(H5N1) viruses and, more recently, A(H7N9) viruses, are two such examples. However, swine are also recognized as a “mixing vessel” for influenza viruses, and over the past two decades, there has been an increase in human cases following exposure to infected pigs. There is clearly, and alarmingly, a vast diversity of zoonotic sources of influenza A viruses that could acquire a transmissible phenotype in humans and cause a pandemic.

What is our readiness today? Many international health agencies and research laboratories collaborate to track influenza virus evolution, evaluate antigenic drift among circulating and vaccine strains, and sequence viral genes to advance surveillance and preparedness. The production of improved vaccines and diagnostic tools, and better access to therapeutic agents represent resources that were not available a century ago. But influenza viruses are moving targets, and a pandemic virus could nevertheless emerge with as little warning in 2018 as in 1918. As evidenced by this current flu season, influenza viruses can rapidly acquire mutations that evade our most recent vaccine formulations. A universal, broadly protective influenza vaccine for seasonal epidemics—a goal of intense research efforts—would improve our preparedness for subsequent pandemics.

How, then, can we best study emerging pandemic threats? Looking to the past, elucidating the role of specific molecular determinants that confer virulence and transmissibility of prior pandemic viruses is one approach. But we must also look to the future. Advances in next-generation sequencing are improving our understanding of virus diversity. Investments in global partnerships and laboratory capacity worldwide are strengthening surveillance networks and diagnostic capabilities, and are also facilitating the identification of new viruses in humans and animals. The recent lifting of the U.S. moratorium on gain-of-function research on potential pandemic viruses further illustrates the contribution of unconventional, but responsible, research strategies to readiness.

Philosopher George Santayana pointed out, “Those who cannot remember the past are condemned to repeat it.” We are no doubt more prepared in 2018 for an infectious disease threat than in 1918. But it is critical to remember that preparation only stems from a global commitment to share data about viral isolates, support innovative research, and dedicate resources to assess the pandemic risk of new and emerging influenza viruses from zoonotic reservoirs.

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