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Readiness for Responding to a Severe Pandemic 100 Years After 1918

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The 1918 H1N1 pandemic caused an unprecedented number of deaths worldwide. The tools to deal with the global emergency were limited; there were insufficient surveillance systems and a dearth of diagnostic, treatment, and prevention options. With continuing focus on pandemic planning, technologic advances in surveillance, vaccine capabilities, and 21st century medical care and countermeasures, we are more prepared for a severe pandemic than people were 100 years ago; however, notable gaps remain.

1918 pandemic; community mitigation; influenza preparedness; medical countermeasures; surveillance

Abbreviations: CDC, Centers for Disease Control and Prevention; NAI, neuraminidase inhibitors; WHO, World Health Organization.

The 1918 influenza pandemic offers the worst-case planning scenario for public health officials because it resulted in unparalleled numbers of deaths. The virus, an A(H1N1) subtype, may have infected half the world's population (1, 2) and caused at least 50 million deaths, according to estimates (3); 675,000 deaths are thought to have occurred in the United States (4). The source of the 1918 H1N1 virus is unknown; avian and swine origins have been proposed (5, 6). Although 3 later pandemics, in 1957, 1968, and 2009, resulted in much lower estimated rates of morbidity and death, the threat of a 1918-like severity pandemic remains, because reports of human infections with novel influenza A viruses (generally of avian or swine origin) that pose pandemic potential have increased in recent years. In particular, Asian lineage avian influenza A (H7N9) viruses caused 1,557 reported human infections and at least 605 deaths during 5 epidemics in China during 2013–2017 (7). Now, 100 years after the 1918 pandemic, is an important time to recall the significant impact of the pandemic and to reflect on the current state of readiness to respond to the next influenza pandemic.

THE PANDEMIC IN 1918

The world situation in 1918 exacerbated the effects of the pandemic. Wartime conditions combined with the intrinsic pathogenicity of the virus to cause tremendous morbidity and death rates. Poor sanitation, overcrowding, and limited health services during World War I facilitated disease transmission (8). Wartime overcrowding was rampant. Camps for troops, hastily built to accommodate 36,000, were soon housing 45,000 young and immunologically naïve soldiers (9). Each day in the summer of 1918, an average of 10,000 US soldiers crammed onto ships bound for France (10). Civilians flooding to cities in support of war industries quickly exceeded available housing capacity (9). With 30% of US physicians engaged in military service, medical personnel were in short supply when the pandemic struck (11).

Multiple, closely spaced pandemic waves, overwhelming the susceptibility of healthy young adults, and lack of specific medical countermeasures contributed to the pandemic's toll. North America experienced herald waves in February through May 1918; in Europe, they occurred from May through July 1918 (12). The second wave, which caused the greatest number of deaths (8), began in August 1918 and, by the end of January 1919, had spread across the globe (13). A third pandemic wave arose in early 1919, only 10 months after the first, and some historians also claim that a fourth wave occurred in early 1920 (14). During the 1918 pandemic, the death rate was high among young adults aged 20–40 years, with peak numbers of deaths in this age group occurring at age 28 years (15).

Treatment for influenza and its complications was mostly supportive care (14). Palliatives from pharmacies and vendors were encouraged, if not presented as cures. No antivirals or antibiotics were available; penicillin was not discovered until 1928 (16). One potentially effective therapy for reducing the risk of death

was use of convalescent sera collected from patients after their infection and administered to patients with current infection (17). Many more physicians, however, attempted to treat patients with "vaccines" (18). At the time, *Haemophilus influenzae* was the presumed etiologic agent for influenza, referred to as Pfeiffer's bacillus. Vaccines were made from culture of the bacillus and may have been effective at reducing some secondary bacterial coinfections.

The exceptional severity from the 1918 pandemic influenza virus prompted implementation of community mitigation measures. With no national strategy or support from the federal government, specific measures, the timing of their initiation, and their duration varied between cities. Of 43 US cities studied, however, all used nonpharmaceutical measures during the second pandemic wave, including school closures, bans on public gatherings, and isolation or quarantine orders (19). Cities that promptly implemented nonpharmaceutical interventions experienced delayed and reduced peak death rates compared with cities that implemented interventions later (19).

The virulence of the 1918 H1N1 virus intensified the situation. Epidemiologic parameters of the 1918 pandemic, which include an attack rate of 28% (20) and an estimated basic reproduction number of 1.8 (21), were similar in subsequent influenza pandemics of 1957 and 1968. However, the estimated case fatality proportion of 1.7% in the 1918 pandemic (22) was more than 10 times higher than in the 1957 and 1968 pandemics. Pandemic influenza in 1918 often presented with an unusually severe and swift clinical course. Disease frequently progressed to extensive organ involvement (23), primary viral pneumonia (24), and secondary bacterial pneumonia and empyema (25). Some military physicians reported a rapid clinical course, with death occurring within 24–48 hours after hospital admission (26). Pneumonia was the cause of death for the vast majority of the deceased (15). The unprecedented death rate exceeded the capacity of many morgues and funeral homes, and bodies were often "stacked like cord wood" (9) in the halls of both military and civilian hospitals. Ultimately, the death toll, particularly among previously healthy young adults, reduced life expectancy in the United States by 12 years (27).

READINESS IN 2018 FOR A SEVERE PANDEMIC

Advances over the past century have clearly improved global preparedness to respond to an influenza pandemic. We now have advanced capabilities in prevention, surveillance, diagnostics, and treatments that were unknown 100 years ago, as well as a myriad of tools for pandemic response planners. However, despite these achievements, gaps remain in our response readiness to a severe influenza pandemic.

Surveillance

The World Health Organization (WHO) Global Influenza Surveillance and Response System currently includes 6 WHO Collaborating Centers for Reference and Research on Influenza (in Australia, China, Japan, the United Kingdom, and the United States), 4 Essential Regulatory Laboratories (in Australia, Japan, the United Kingdom, and the United States), and 143 National Influenza Centers in 114 WHO Member States (28). Laboratories within this network routinely test respiratory specimens to detect seasonal and emerging novel influenza A viruses of animal origin that have infected humans, and to assess the genetic and antigenic characteristics of these viruses. According to WHO's International Health Regulations, countries must notify WHO within 24 hours of any case of human infection caused by a new influenza A virus subtype,because it may constitute a public health emergency of international concern (29). In 2004, the US Centers for Disease Control and Prevention (CDC) began an international capacity-strengthening initiative, providing a 5-year period of financial support for capacity building to improve laboratory diagnostics and sentinel surveillance of influenza-like illness and severe acute respiratory infection in 39 partner countries. The program substantially increased laboratory and sentinel surveillance capabilities, and most participating countries leveraged the influenza surveillance platforms to detect other pathogens. Of the 39 countries, 36 transitioned from the initial 5-year period of financial support to the program's second 5-year period, during which financial support is incrementally reduced (30).

Influenza surveillance is multifaceted and includes the collection and analyses of data to monitor disease severity, antiviral resistance, and the evolution and circulation of influenza viruses around the globe. In the United States, the CDC analyzes data on influenza activity through multiple surveillance sources: virus characterization from specimens collected, outpatient illness, deaths among adults, population-based hospitalizations, and reports of geographic spread of influenza (31). Since 2013, "right-size" calculators have been available through a collaboration between the CDC and theAssociation of Public Health Laboratories. These calculators assist states in determining the optimal number of specimens required for desired confidence levels of virologic surveillance (32). In addition, novel influenza A virus infections, as well as pediatric influenza-caused deaths, are included in the list of nationally notifiable conditions that are reported to the CDC (33). The agency also coordinates with the US Department of Agriculture in conducting surveillance for influenza A viruses in livestock, including poultry and swine, and assists the US Department of Agriculture in identifying, sequencing, and confirming laboratory findings. In addition, the US Geological Survey National Wildlife Health Center coordinates with the US Department of Agriculture, the US Fish and Wildlife Service, and state wildlife agencies to implement enhanced investigations of deaths and surveillance in wild birds (34). Together, these surveillance activities promote better understanding of circulation of influenza A viruses among animal hosts. Coordinated surveillance of influenza viruses in animals and humans subsequently can inform pandemic risk assessment and prepandemic vaccine development.

However, gaps remain in influenza surveillance. Data are incomplete or lacking in many low- and middle-income countries with limited influenza testing capacity (35). Building and strengthening laboratory capacity to detect influenza viruses in low-resource settings, and facilitating faster, less complicated mechanisms for specimen sharing could improve global influenza surveillance. In addition, improved surveillance of influenza A viruses circulating among birds and swine will help monitor the evolution of novel influenza A viruses and related viruses that might be of public health concern.

Diagnostics

Several different influenza tests are now available to detect influenza virus infection in respiratory tract specimens, thus improving diagnosis and facilitating surveillance. Simple-to-use rapid influenza antigen detection tests have been available for point-of-care use for many years and can identify influenza virus antigens within 15 minutes. However, for most rapid tests performed in a doctor's office to detect influenza viruses, the sensitivity ranges from approximately 50% to 70%. In 2017, the US Food and Drug Administration reclassified rapid influenza diagnostic tests to require improved accuracy and, notably, higher sensitivity (36). Even so, molecular assays that detect influenza virus nucleic acids are more accurate, with higher sensitivity (90%–100%) and specificity (95%–100%). Newer, low-complexity tests that detect nucleic acids in respiratory specimens in under 30 minutes are available, some for use in outpatient settings (37). Moderate- and high-complexity molecular assays, with very high accuracy, such as reverse transcriptase–polymerase chain reaction, may require 45 minutes to several hours for results. Some of these tests can provide additional details about positive specimens, such as identifying influenza A virus subtypes.

An important early need in a pandemic is getting test reagents quickly to laboratories to verify the emergence and progression of the virus around the globe. The International Reagent Resource, established by the CDC in 2008, provides registered users in domestic and global laboratories with the reagents needed to perform reverse transcriptase–polymerase chain reaction assays and identify seasonal influenza A and B viruses and novel influenza A viruses. Success of the program was evident in 2009 when, less than 2 weeks after initial recognition of the 2009 H1N1 pandemic influenza virus, the CDC developed, and the International Reagent Resource began distributing, a new, approved pandemic influenza H1N1 polymerase chain reaction assay to public health laboratories throughout the United States and globally, enabling them to track the spread of the pandemic virus (38). In 2013, the International Reagent Resource distributed H7N9 diagnostic kits to 47 US states within 2 weeks of virus identification and, within 2 months, had shipped 194 diagnostic kits to international laboratories (Erica Guthrie, Influenza Division, National Center for Immunization and Respiratory Diseases, CDC, unpublished data, 2014).

Other tests used to detect and characterize influenza viruses in respiratory specimens include virus culture and next-generation sequencing. Some public health laboratories perform virus isolation using tissue cell culture to facilitate detailed virus characterization, including antigenic comparison with vaccine virus strains. Next- generation sequencing identifies influenza virus genomes. The CDC and its National Influenza Reference Centers use next-generation sequencing to characterize all respiratory specimens tested. Genetic sequence data from other WHO Collaborating Centers and multiple academic and other sources are made available in publicly available data repositories (e.g., Global Initiative on Sharing All Influenza Data (GISAID), GenBank). Finally, genetic and phenotypic functional assays are available to identify if an influenza virus has developed antiviral resistance.

Diagnostic capability in many low- and middle-income countries, however, remains inadequate. Increasing this capability not only will improve our understanding of the burden of influenza in these locations but also will improve global surveillance data and pandemic preparedness.

Prevention

Before vaccine against the specific emerging pandemic virus strain is available, nonpharmaceutical interventions can offer strategies for persons and communities to help slow spread of the virus. Guidelines for use of these strategies were published by the CDC in 2007 (39); in 2017, a revised version, including an updated evidence base, became available. Nonpharmaceutical strategies include personal protective measures for everyday use and pandemic use, community measures to increase social distancing, and environmental measures, such as surface-cleaning measures, to reduce the transfer of viruses. The revised guidelines include a section on community-engagement principles, as well as links to 6 supplemental planning guides for specific community settings (40).

In the last 100 years, numerous vaccines have become available for influenza prevention. In the United States, national vaccine policy recommends influenza vaccination annually for everyone older than age 6 months. There are multiple types of vaccine that use different inactivated, live-attenuated, and egg-free formulations (41). Recent efforts through WHO's Global Action Plan for Influenza Vaccines and the Pandemic Influenza Preparedness framework supported efforts to increase vaccine manufacturing and laboratory capacity for identifying viruses for use in vaccines (42). The global pandemic influenza vaccine production capacity in 2015 was estimated to be 6.4 billion doses—a record level, but not enough to provide the potential need for 2 doses for even half the world's population. The current timeline for vaccine production also limits the usefulness of pandemic vaccine, as reflected in 2009, when the bulk of pandemic vaccine was not available until after the peak of the pandemic. However, increased use of new vaccine formulations that do not rely on growing viruses in eggs, such as cell-based vaccine and recombinant protein vaccine, will reduce the time required for vaccine manufacturing. In addition, further expansion of seasonal influenza vaccine manufacturing capacity worldwide, and continued increases in use of vaccine, will facilitate pandemic vaccine production and global access to pandemic vaccines.

Since 2010, a source that has informed decisions to manufacture and stockpile prepandemic vaccines is the CDC's Influenza Risk Assessment Tool (43). The Influenza Risk Assessment Tool uses 10 risk elements to generate a summary risk score for emerging novel influenza A viruses and other viruses of potential public health concern. The score answers 2 questions. First, what is the risk that a virus not currently circulating in humans has the potential for sustained human-to-human transmission? Second, if the virus does establish ability for sustained human-to-human transmission, what is the potential for substantial impact on public health? Influenza Risk Assessment Tool scores provide input into prepandemic preparedness decisions, such as selection of candidate vaccine viruses and decisions for manufacturing vaccines for the Strategic National Stockpile supported by the Biological

Advanced Research and Development Authority of the US Department of Health and Human Services (43).

Many challenges remain to improving influenza vaccines. Current seasonal influenza vaccines, at best, are only moderately effective in preventing illness and often have low effectiveness. Greater monitoring of vaccine effectiveness is needed to better inform incremental improvements in current influenza vaccines. A more broadly protective and longer-lasting (i.e., "universal") vaccine could decrease the current need for frequent formulation change and improve prevention of influenza worldwide, especially in low-resource and middle-income countries (44). Rapid development of vaccine candidates, accelerated clinical trials, and reducing the time required to formulate and distribute pandemic vaccine can reduce pandemic morbidity and deaths. Therefore, reducing the current pandemic influenza vaccine availability timeframe from 20 to 12 weeks is a key priority in the 2017 Update of the Health and Human Services Pandemic Influenza Plan (45).

Treatment

Antiviral medications were first available for pandemic use in 1968, when amantadine was used to treat pandemic influenza A (H3N2) virus infections. Both amantadine and a related drug, rimantadine, are no longer recommended because of widespread antiviral resistance among circulating seasonal influenza A viruses. In the late 1990s, neuraminidase inhibitors (NAIs) were approved for use. These drugs block release of influenza virus particles from infected cells and are the predominant therapy used today. Early initiation of treatment (ideally within 2 days of illness onset) with NAIs reduces symptom duration and may help reduce the risk of some influenza complications (46–49). Three antiviral drugs were recommended by the CDC for the 2017/2018 season: oseltamivir for oral administration in all ages (available as a generic version or under the trade name Tamiflu (Genentech, San Francisco, California)), zanamivir (trade name Relenza (GlaxoSmithKline, Research Triangle Park, North Carolina)) for oral inhalation in persons age 7 years or older, and peramivir (trade name Rapivab (Seqirus, Summit, New Jersey)) for intravenous administration, which is now approved for children age 2 years or older (50).

Better antiviral treatments are needed. Influenza viruses are continuously evolving, and resistance to NAIs can emerge during treatment. There is an urgent need for more effective antivirals with different mechanisms of action than that of NAIs. New antivirals will also allow combination treatment with NAIs. Recently, a new antiviral that works differently than NAIs, by inhibiting influenza virus polymerase and blocking virus replication, was approved in Japan (51). The greatest need, however, is for drugs with efficacy in treating severe influenza, particularly in hospitalized patients. Immunomodulators and immunotherapeutics are in development, including monoclonal and polyclonal antibodies and hyperimmune plasma (52–54). Greater availability and lower costs of generic oseltamivir will likely facilitate access in low- and middle-income countries. However, cost considerations could pose challenges to the availability of new therapeutics outside of developed countries.

In addition to antiviral medications, clinical management of severe influenza is based on supportive care of complications (e.g., supplemental oxygen, antibiotics for secondary invasive bacterial coinfection) and advanced organ support (e.g., lung-protective ventilator strategies and extracorporeal membrane oxygenation for refractory hypoxemia caused by the acute respiratory distress syndrome, renal replacement therapy for kidney failure, vasopressors for refractory shock) for critically ill patients, as highlighted during the 2009 H1N1 pandemic (55–58). According to recent estimates of global deaths for seasonal influenza epidemics and the 2009 H1N1 pandemic, the death rate was highest in sub-Saharan Africa (59–61). However, critical care capacity is insufficient throughout much of the globe, and building and strengthening clinical capacity, especially for low-resource countries, such as in sub-Saharan Africa, is vitally important.

Planning and preparedness efforts are widespread and ongoing, on a scale likely not imagined in 1918. Pandemic plans have been developed by a variety of stakeholders, including nations, states, counties, cities, and businesses. WHO has published essential steps for developing a national pandemic plan, as well as a checklist for pandemic influenza risk and impact management (62, 63). In the United States, the Department of Health and Human Services published an updated 2017 Pandemic Influenza Plan that highlighted successes since the 2005 Pandemic Influenza Plan and emphasized needed improvements (45). However, the majority of countries reported by WHO still have no, or no publically available, national plan for pandemic preparedness and risk management (64).

In addition to pandemic plans, many supplementary materials are now available to planners. In 2014, the CDC published a framework for pandemic intervals to provide an organizing structure for pandemic events (65). The framework identifies 6 pandemic intervals, as well as a variety of indicators and interventions, within a hypothetical pandemic curve. Intervals include investigation and recognition of a novel influenza A virus with sustained human-to-human transmission, initiation, acceleration, and deceleration of a resultant pandemic wave, and preparation for subsequent pandemic waves. Assessments, interpretations, and findings define the transmission points between the intervals and are used to initiate decisions and actions (65).

Pandemic severity is one example of an indicator that can help guide public health decision-making. A Pandemic Severity Assessment Framework is now available that uses data to assign a severity score and a transmissibility score to pandemics (66). Early in a pandemic, when limited data are available, scores are based on dichotomous ratings: low-moderate or moderate-high. As additional data become available, more discriminating transmissibility (range, 1–5) and severity (range, 1–7) scores can be assigned. Scores are then plotted to characterize the potential pandemic impact in relation to previous pandemics or seasonal epidemics, informing appropriate breadth and depth of response activities.

Mitigating the impact of an emerging pandemic depends on rapid availability of treatment, clinical support, and vaccines. Many countries maintain stockpiles of drugs and other countermeasures. In the United States, state and federal government stockpiles are in place, and prepandemic vaccines, ventilators, respiratory protective devices and personal protective equipment, and antiviral drugs can be distributed rapidly (67). In addition, diagnostic tests that can identify novel influenza A virus infections are poised to be distributed globally by the CDC's International Reagent Resource.

CONCLUSION

Despite improvements since 1918, governments and health care systems remain inadequately prepared for the impact of a 1918-like severe influenza pandemic. A significant focus on improving global preparedness for infectious disease threats has occurred through implementation of the Global Health Security Agenda and associated efforts (68). Beginning with the revision of the International Health Regulations in 2005, milestones were set for countries to achieve greater response capacity for public health emergencies. However, by 2016, only one-third of countries were in compliance. Through the coordinated multisectorial work on global health security and other international efforts, new external reviews of a country's response capacity are underway as part of the WHO Joint External Evaluation process. With these new tools and coordinated intergovernmental activities, overall base capacity of responding to global health threats may be improved. In addition, targeted efforts for detecting and responding specifically to influenza threats through WHO's Global Influenza Surveillance and Response System/Pandemic Influenza Preparedness framework and country support from the CDC and others can provide a path toward greater pandemic preparedness.

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