100 Years of Medical Countermeasures and Pandemic Influenza Preparedness

The 1918 influenza pandemic spread rapidly around the globe, leading to high mortality and social disruption.

The countermeasures available to mitigate the pandemic were limited and relied on nonpharmaceutical interventions. Over the past 100 years, improvements in medical care, influenza vaccines, antiviral medications, community mitigation efforts, diagnosis, and communications have improved pandemic response.

A number of gaps remain, including vaccines that are more rapidly manufactured, antiviral drugs that are more effective and available, and better respiratory protective devices. (*Am J Public Health.* 2018;108:1469–1472. doi:10.2105/AJPH.2018.304586)

Barbara J. Jester, RN, MSN, Timothy M. Uyeki, MD, MPH, MPP, Anita Patel, PharmD, MS, Lisa Koonin, MN, DrPH, MPH, and Daniel B. Jernigan, MD

See also Parmet and Rothstein, p. 1435.

The 1918 H1N1 influenza pandemic was unprecedented, with rapid global spread and high mortality. The potential for an influenza pandemic remains a constant public health threat. If a pandemic like the one in 1918 were to happen today, it would be likely to overwhelm the health care infrastructure and would require significant increases in the production, supply, and distribution of potentially life-saving pharmaceuticals and medical supplies.

The devastating pandemic that emerged in 1918 caused at least 50 million deaths worldwide, 675 000 of which occurred in the United States.[1] At that time, there were very limited countermeasures to mitigate the global spread of or treat infections from the 1918 H1N1 virus. There were no diagnostic tests available to confirm infection, no influenza vaccine available to prevent infection, and no antiviral medications that could reduce severity and duration of symptoms. Critical care measures, such as intensive care support or mechanical ventilators, were not available. The 1918 pandemic predated antibiotics, leaving those infected with limited treatment options for secondary bacterial coinfections.

Since 1918, the world has experienced three subsequent pandemics. The estimated global mortality associated with these events was significantly lower, with approximately 1 million for the 1957 H2N2 and 1968 H3N2 pandemics and fewer than 0.3 million for the first year of the 2009 H1N1 pandemic.[1] Despite the lower impact of recent pandemics, the potential for a pandemic with very high severity remains. Public health officials are watching one avian influenza A virus, A (H7N9) in China, very closely. Since 2013, it has caused a high number of human infections, 1567 so far, with a case–fatality proportion of around 40%.[2]

While advances in medical care and countermeasures contributed to a reduction in deaths in the past three pandemics, and although these measures are widely available today, a novel influenza A virus could abruptly change to become a more human-adapted virus, spreading efficiently from person to person and causing significant morbidity and mortality worldwide. Given these current risks, the centenary of the 1918 H1N1 pandemic is an appropriate time to review the state of countermeasures then, highlight progress made over time to the current state, and identify remaining gaps to better prepare us for the next pandemic.

CONTEXT AND COUNTERMEASURES IN 1918

Multiple factors contributed to morbidity and mortality of the 1918 H1N1 pandemic. Virus transmission was facilitated by rampant overcrowding in military training camps and most major cities. Tightly spaced waves of respiratory disease, three within ten months,[3] overwhelmed available resources and left little time to replace medical personnel who had succumbed to the disease. The pandemic created a unique W-shaped mortality curve with high frequency of secondary pneumonia and subsequent mortality among young adults.[4]

The arsenal of available medical countermeasures to treat pandemic influenza virus infections in 1918 was quite basic and largely limited to supportive care. In the absence of antibiotics and antivirals, over-the-counter

ABOUT THE AUTHORS

Barbara J. Jester is a Battelle contractor working for the Influenza Division at Centers for Disease Control and Prevention (CDC), Atlanta, GA. Timothy M. Uyeki is chief medical officer for the Influenza Division at CDC. Anita Patel is the medical care and countermeasures team lead for the Influenza Coordination Unit at CDC. Lisa Koonin is deputy director of the Influenza Coordination Unit at CDC. Daniel B. Jernigan is director of the Influenza Division at CDC.

Correspondence should be sent to Daniel B. Jernigan, MD, MPH, Director, Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A20, Atlanta, GA 30329 (e-mail: djernigan@cdc.gov). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

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remedies were commonly employed. These included aspirin, quinine, ammonia, turpentine, salt water, topical rubs, inhaled substances for congestion, and Bovril (a thick, salty meat extract).[5] Some physicians collected sera from recovered patients and injected this convalescent serum into patients with active infection. A meta-analysis of publications reporting results from this strategy suggested that recipients of convalescent serum may have experienced reduced risk of death.[6] Nonstandardized vaccines were developed and recommended by a large number of physicians. These vaccines were given primarily to protect against Pfeiffer's bacillus, later named *Haemophilus influenzae*, as the medical community commonly believed this bacillus to be the cause of influenza.[7] These vaccines could only have been effective in preventing secondary infections, as testing of the earliest influenza vaccine would not begin for more than a decade.[8]

In the absence of effective specific drugs and vaccines, nonpharmaceutical countermeasures were critical. Fresh air and sunshine were espoused by some, including the Surgeon General of the Massachusetts State Guard on the basis of his experience with influenza on ships in East Boston.[9] School closures, with and without additional public-gathering bans, were commonly employed.[10]

ACCOMPLISHMENTS AFTER 1918 AND CURRENT SITUATION

Since 1918, improvements in surveillance, diagnostics, situational awareness tools, community mitigation science, and communication all leave us better equipped to prepare for and respond to an influenza pandemic. In addition, significant progress in diagnostic and pharmaceutical research and development has brought key products to market. There are now many medical countermeasures available for diagnosis, prevention, and treatment of pandemic influenza.

Diagnostics

Following the recognition of the influenza virus in 1931,[11] a means for diagnosing and studying influenza virus infection became available. Culture in eggs and cells, with use of influenza-specific direct fluorescent antibodies, served as the primary means for diagnosing influenza for many years.[12] Now, a wide variety of laboratory tests is available to confirm influenza virus infection. Point-of-care influenza tests, first introduced in the 1990s, include (1) rapid immunoassays with low to moderate sensitivity (50%–70%) that provide results in 15 to 20 minutes and (2) rapid molecular assays, more accurate than immunoassays, that can yield results in 15 to 30 minutes.[13] Commercial, clinical, academic, and hospital laboratories, as well as public health laboratories, now perform moderate- and higher-complexity tests, including virus culture and other molecular assays. Using information from these clinical sources, along with high-complexity polymerase chain reaction testing at 64 public health laboratories, surveillance is able to detect seasonal, novel, and emerging pandemic influenza viruses in the United States much earlier and more accurately than in the past.

In addition, the Centers for Disease Control and Prevention (CDC) and a subset of public health laboratories routinely perform next-generation genetic sequencing on all respiratory specimens received. The CDC and state health departments use these virologic data to monitor influenza virus characteristics, disease activity, geographic spread, virulence, antiviral effectiveness, and vaccine effectiveness, as well as to develop candidate vaccine viruses.[14] However, confirmatory diagnostic testing is not required to initiate treatment, as antiviral treatment is most effective when begun as close to illness onset as possible.

Vaccines

The first clinical trials of influenza vaccines began in the 1930s, and, by 1942, large studies of inactivated influenza vaccines were underway.[8] Influenza vaccination is now considered the first and most important step in protecting against influenza viruses. Since 2010, the US Advisory Committee on Immunization Practices has recommended annual influenza vaccination for almost all individuals aged 6 months or older. For the 2017–2018 influenza season, multiple influenza vaccine formulations were available, including standard dose, high dose, adjuvanted, and two more recently developed vaccines made without eggs: a cell-based manufactured vaccine and a recombinant protein vaccine. These latter two vaccines represent new technologies that may allow for faster vaccine production in the event of a pandemic. Manufacturers have indicated that as many as 151 million to 166 million doses of injectable influenza vaccine were made available for the 2017–2018 season.[15] Influenza viruses are continually evolving; thus, influenza vaccines must be regularly updated. The "warm base" of seasonal influenza vaccine manufacturing capability, now with greater capacity and newer technologies, facilitates pandemic vaccine production.

Antiviral Medications

The first drug approved for treatment of influenza was amantadine. This drug was approved in 1966 but was not widely used until after the 1968 H3N2 pandemic.[16] Since then, a similar drug, rimantidine, was approved, but, beginning in 2005, both drugs are no longer recommended for treatment of influenza A viruses because of the high prevalence of resistance.[17] A new class of antiviral drugs, the neuraminidase inhibitors, was first approved in 1999 with the release of oseltamivir and zanamivir.[18] These medications can lessen the duration of influenza symptoms and may help prevent serious complications, especially when treatment is started early after illness onset. The CDC recommended three US Food and Drug Administration–approved antiviral medications for treatment of influenza during the 2017–2018 season.[19] In addition to antivirals for influenza, physicians can now prescribe a wide spectrum of antimicrobial drugs for treatment of secondary bacterial coinfections.

Health Care Infrastructure and Personal Protective Equipment

The 1918 H1N1 pandemic overwhelmed medical services. Lacking medical countermeasures, supportive care was all that was available, yet the supply of physicians, nurses, support staff, beds, linens, and equipment was inadequate to address even this need. Gymnasiums, parish halls, and state armories were used to house patients. Medical school graduations and board examinations were expedited and full staff duties were assigned to student nurses and physicians.[20] Now patients can benefit from the many advances in medical care and supplies that have appeared over the past century. For example, intensive care units provide exceptional monitoring and life-saving specialty care for patients with severe complications from influenza. Mechanical ventilators offer critical respiratory support for patients with respiratory failure and compromised lung function.

In addition, personal protective equipment now protects health professionals by decreasing exposure to respiratory viruses. Medical personnel can use respiratory protective devices (e.g., N95 filtering facepiece respirators, personal powered air-purifying respirators) and other personal protective equipment (e.g., gowns, gloves, goggles, face shields) to protect themselves from respiratory diseases. They can also place modern surgical masks on patients to control viral transmission at the source.

Hospital Preparedness and Countermeasure Stockpiles

In 1918, the United States was completely unprepared for the impact of the pandemic. Even worse, government officials initially stifled communication about the rapidly spreading pandemic to avoid the appearance that the country's war effort might be compromised.[21] In 2018, coordination and communication for pandemic preparedness and response are supported globally by the World Health Organization (WHO) and by the US government with the Department of Health and Human Services (HHS) in the lead. Large efforts have also occurred to increase access and availability of critical medical countermeasures for pandemic influenza. The CDC's Strategic National Stockpile manages and distributes medical countermeasures, including antiviral medications, ventilators, and personal protective equipment, as well as other life-saving pharmaceuticals and medical supplies. The Stockpile, originally established to support procurement and management of medical countermeasures for responding to terrorism emergencies, has since evolved also to prepare for pandemic influenza and natural disasters. The Stockpile is intended to ensure availability of medical materiel during a public health emergency, such as a pandemic, when local supplies may be depleted.[22]

Pandemic preparedness activities now include advances in access to health care, in addition to medications and supplies. One such initiative involves activation of a national network of nurse triage telephone lines (Flu on Call) to better direct patients to the right level of care and increase access to antiviral drug prescriptions. The CDC and public health partners are exploring whether such triage lines, staffed by trained professionals, could adequately provide information, clinical advice, and access to prescriptions during a pandemic. By helping callers identify the most appropriate site for their care, these triage lines might leverage outpatient resources and reduce surge demand on emergency departments and the health care system.[23]

Finally, the HHS Office of the Assistant Secretary for Preparedness and Response oversees a Hospital Preparedness Program to promote readiness in the health care delivery system for situations that exceed day-to-day capacity and capability. The program intends to improve patient outcomes, minimize the need for federal and supplemental state resources during emergencies, and enable rapid recovery.[24] Health care coalitions are a major element of the initiative. These coalitions, which include health care and response organizations, offer an organizing framework for a pandemic response and coordinated regional health care responses for defined geographic locations.

REMAINING GAPS

In 2018, as the world continues to become more crowded and connected, the potential impact of a severe influenza pandemic underscores the continued need for advances in pandemic countermeasures. The rising world population (1.8 billion in 1918 and 7.6 billion in 2018),[25] many residing in urban areas, increases infection transmission potential. In addition, swine and poultry populations have been increased to meet food and protein demands worldwide, expanding the number of potential intermediate hosts between the aquatic bird reservoir of influenza A viruses and humans. Global travel has also increased, further facilitating worldwide spread of respiratory viruses. To improve pandemic preparedness, it will be necessary to continue enhancing the capacity of global partners to detect and respond to influenza outbreaks. In particular, surveillance and response capacity should be strengthened in developing countries for monitoring influenza A viruses not only in humans but also in birds and swine.

Improving diagnostics will enhance pandemic preparedness. Highly accurate, simple, and inexpensive influenza tests with a long shelf life that produce rapid and reliable results will facilitate clinical management of influenza in all health care settings. Researchers should also investigate easier and faster methods for confirming novel influenza A virus infections.

Public health officials and vaccine manufacturers should continue current efforts to improve the timeliness of pandemic vaccine production and methods of distribution, as vaccination is the most effective preventive medical intervention. During the 2009 influenza pandemic, the first doses of pandemic vaccine were not available until 26 weeks after the decision to manufacture a monovalent vaccine, resulting in most vaccination in the United States occurring after the peak of illness. Reducing the time required to produce a pandemic vaccine to 12 weeks is a key priority of HHS.[26]

In addition to pandemic vaccines, new therapeutics that are much more effective than currently available antiviral medications are urgently needed, especially for treatment of severe disease in hospitalized influenza patients. Products with different mechanisms of action, needed to offset the threat of influenza viruses developing resistance to currently available antivirals, are being tested.[27] Enhancing the research and development of novel therapeutic options and making these products more widely available (e.g., through pharmacies, mail order) and less costly are high federal priorities included in the 2017 update to the HHS Pandemic Influenza Plan.[26]

Many countries will require greater clinical capacity, including mechanical ventilators. There is also a need to continue advancements for antimicrobials and respiratory support technology. In addition, most countries still need a robust pandemic plan.

The WHO recommends that all countries develop national pandemic influenza preparedness and response plans. However, of the 194 countries reported by WHO, 101 have no, or no publically available, national plan for pandemic preparedness and risk management; 68 countries have plans that date from 2009 or before, while only 25 countries have published or revised plans since 2010.[28]

CONCLUSIONS

The 1918 H1N1 pandemic has been the worst-case scenario for pandemic planners, as it produced the greatest influenza mortality in recorded history and the greatest mortality of any infectious disease outbreak of the 20th century. Over the past 100 years, there have been major advances in surveillance, diagnostics, medical care, and communication. These advances now enable us to prevent infection with both medical countermeasures and nonpharmaceutical interventions, as well as detect influenza viruses; monitor morbidity, mortality, and disease spread; treat infected patients; and manage severe complications. However, the risk of pandemic influenza remains, as evidenced by emergence of Asian lineage avian influenza A (H7N9) virus and other novel influenza A viruses. Planning must continue with an emphasis on augmenting preparedness and leveraging advancements in research, development, technologies, and systems. Improving prevention and control of seasonal influenza will result in better response capability for pandemic influenza. Pandemic planners must identify and address remaining gaps to minimize the effects of future pandemics and especially to prevent mortality on the scale seen in 1918. AJPH

CONTRIBUTORS

All of the authors contributed equally to this article.

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REFERENCES

1. Centers for Disease Control and Prevention. Pandemic influenza. 2017. Available at: https://www.cdc.gov/flu/pandemic-resources/index.htm. Accessed November 8, 2017.

2. Kile JC, Ren R, Liu L, et al. Update: Increase in human infections with novel Asian lineage avian influenza A(H7N9) viruses during the fifth epidemic—China, October 1, 2016–August 7, 2017. *MMWR Morb Mortal Wkly Rep*. 2017; 66(35):928–932.

3. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. *Emerg Infect Dis*. 2006;12(1):15–22.

4. Frost W. The epidemiology of influenza. *JAMA*. 1919;73(5):313–318.

5. Jivraj N, Butler A. The 1918–19 influenza pandemic revisited. *J R Coll Physicians Edinb*. 2013;43(4):347–352.

6. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med*. 2006;145(8):599–609.

7. Leary T. The use of influenza vaccine in the present epidemic. *Am J Public Health (N Y)*. 1918;8(10):754–768.

8. Barberis I, Myles P, Ault SK, Bragazzi NL, Martini M. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. *J Prev Med Hyg*. 2016; 57(3):E115–E120.

9. Brooks WA. The open air treatment of influenza. *Am J Public Health (N Y)*. 1918; 8(10):746–750.

10. Markel H, Lipman HB, Navarro JA, et al. Nonpharmaceutical interventions implemented by US cities during the 1918–1919 influenza pandemic. *JAMA*. 2007;298(6):644–654.

11. Shope RE. Swine influenza: I. Experimental transmission and pathology. *J Exp Med*. 1931;54(3):349–359.

12. Kim DK, Poudel B. Tools to detect influenza virus. *Yonsei Med J*. 2013;54(3): 560–566.

13. Centers for Disease Control and Prevention. Diagnosing flu. 2018. Available at: https://www.cdc.gov/flu/about/qa/testing.htm. Accessed January 2, 2018.

14. Centers for Disease Control and Prevention. Overview of influenza surveillance in the United States. 2018. Available at: https://www.cdc.gov/flu/weekly/overview.htm. Accessed January 9, 2018.

15. Centers for Disease Control and Prevention. Key facts about seasonal flu vaccine. 2018. Available at: https://www.cdc.gov/flu/protect/keyfacts.htm. Accessed January 2, 2018.

16. Amantadine and influenza. *Lancet*. 1969;2(7629):1055–1056.

17. Deyde VM, Xu X, Bright RA, et al. Surveillance of resistance to adamantanes among influenza A(H3N2) and A(H1N1) viruses isolated worldwide. *J Infect Dis*. 2007;196(2):249–257.

18. Neuraminidase inhibitors for treatment of influenza A and B infections. *MMWR Recomm Rep*. 1999;48(RR-14): 1–9.

19. Centers for Disease Control and Prevention. What you should know about flu antiviral drugs. 2018. Available at: https://www.cdc.gov/flu/antivirals/whatyoushould.htm. Accessed January 2, 2018.

20. Schoch-Spana M. "Hospital's full-up": the 1918 influenza pandemic. *Public Health Rep*. 2001;116(suppl 2):32–33.

21. Barry JM. *The Great Influenza: The Epic Story of the Deadliest Plague in History*. New York, NY: Penguin Books; 2005.

22. Centers for Disease Control and Prevention. Strategic National Stockpile. 2017. Available at: https://www.cdc.gov/phpr/stockpile/history.htm. Accessed June 2, 2017.

23. Koonin LM, Hanfling D. Broadening access to medical care during a severe influenza pandemic: the CDC nurse triage line project. *Biosecur Bioterror*. 2013;11(1):75–80.

24. Assistant Secretary for Preparedness and Response. Hospital Preparedness Program (HPP). Department of Health and Human Services. 2017. Available at: https://www.phe.gov/preparedness/planning/hpp/pages/default.aspx. Accessed November 20, 2017.

25. United Nations Department of Economic and Social Affairs Population Division. World Population Prospects: The 2017 Revision. United Nations. 2017. Available at: https://esa.un.org/unpd/wpp/DataQuery. Accessed November 8, 2017.

26. US Department of Health and Human Services. Pandemic influenza plan: 2017 Update. Available at: https://www.cdc.gov/flu/pandemic/resources. Accessed November 8, 2017.

27. Amarelle L, Lecuona E, Sznajder JI. Anti-influenza treatment: drugs currently used and under development. *Arch Bronconeumol*. 2017;53(1):19–26.

28. World Health Organization. National Plans for Pandemic Preparedness and Risk Management. 2017. Available at: https://extranet.who.int/sph/influenza-plan. Accessed November 22, 2017.