Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

JAMA. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

JAMA. 2018 August 28; 320(8): 755–756. doi:10.1001/jama.2018.8113.

Gaps in the Clinical Management of Influenza:

A Century Since the 1918 Pandemic

Timothy M. Uyeki, MD, MPH, MPP,

Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.

Robert A. Fowler, MD, MDCM, MSc,

Department of Critical Care Medicine and Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

William A. Fischer II, MD

Division of Pulmonary and Critical Care Medicine, University of North Carolina at Chapel Hill.

This year marks the centennial of the devastating 1918 influenza A(H1N1) pandemic, which killed an estimated 50 million people worldwide. Prevention and control activities were limited in 1918 because global surveillance did not exist, influenza viruses were not yet discovered, and no influenza vaccines had been developed. Diagnostic tests for influenza were unavailable prior to isolation of influenza viruses in the 1930s, so spread of the pandemic virus was tracked by news reports of increased respiratory disease and related deaths. Establishment of the World Health Organization's Global Influenza Surveillance Network in 1952 has contributed substantially to coordinated surveillance, vaccine development, and influenza vaccine strain selection.

Pandemic influenza vaccine was not available until the 1957 influenza A(H2N2) pandemic, so prevention and control efforts in 1918 relied on nonpharmaceutical interventions, including isolation and quarantine, social distancing, public gathering bans, school closures, and mask wearing. Treatment options were limited: antivirals were not available until the 1968 influenza A(H3N2) pandemic; antibiotics for secondary bacterial infections had not yet been discovered; and organ supporting care strategies, other than supplemental oxygen, did not exist until the mid-1950s. While advances in influenza surveillance and availability of influenza vaccines have been increasingly effective, major gaps remain in the clinical response to seasonal influenza epidemics and pandemics.

During the 2009 influenza A(H1N1) pandemic, rapid antigen tests had suboptimal sensitivity in detecting the pandemic virus, frequently yielding false-negative results. Clinicians caring for hospitalized patients often had to wait at least one day for reverse

Corresponding Author: Timothy M., Uyeki MD, MPH, MPP, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30329 (tmu0@cdc.gov).

Disclaimer: The views expressed hereinare those of the authors and do not necessarily reflect the official policy of the Centers for Disease Control and Prevention.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

transcriptase-polymerase chain reaction testing results from a referral laboratory. Recently, molecular-based diagnostic tests (including rapid molecular assays) that can detect influenza viral nucleic acids in upper respiratory tract specimens with high sensitivity and specificity have become available in ambulatory and inpatient settings. How-ever, the molecular assays in use in clinical settings do not distinguish between seasonal and novel influenza A viruses of zoonotic origin and cannot specifically identify the next pandemic virus. Clinicians need to work closely with public health laboratories to monitor surveillance data. Development of tests based on next-generation sequencing technology may facilitate more accurate and timely identification of antigenically drifted seasonal influenza viruses, novel influenza A viruses, and viruses with known markers of antiviral resistance. Whether this would ultimately improve health out-comes would need to be determined.

Currently, antiviral treatment of influenza is focused on early initiation of monotherapy with one drug class, neuraminidase inhibitors (NAIs). Randomized clinical trials (RCTs) demonstrated shortened duration of fever and illness in outpatients with uncomplicated influenza who start treatment with the NAI oseltamivir within 2 days of symptom onset compared with placebo.[1,2] A meta-analysis of RCTs involving adults and an observational study of high-risk children and adults reported reduced risk of hospitalization in outpatients treated with NAIs.[1,3] However, enrolling hospitalized patients in RCTs of NAI treatment vs placebo has proved problematic, and challenges remain in identifying optimal end points.[4] Evidence for NAI effectiveness in hospitalized patients with influenza includes observational studies of variable quality. One meta-analysis of observational data from 29 234 hospitalized patients (86% with laboratory-confirmed influenza A(H1N1) pdm09 virus infection) reported survival benefit in NAI-treated adults.[5] However, not all observational studies of NAI treatment have reported benefit in hospitalized patients with influenza, and disagreement exists on the strength of the evidence base and the overall effectiveness of NAIs.[6]

Influenza virus resistance to antiviral drugs can emerge sporadically during or after antiviral treatment, particularly in severely immunocompromised patients. Oseltamivir-resistant influenza A(H1N1) viruses became prevalent worldwide between 2007 and early 2009. These viruses were replaced by the 2009 influenza A(H1N1) pandemic virus (now referred to as influenza A(H1N1)pdm09) which continues to circulate as a seasonal influenza A virus with sporadic detection of oseltamivir resistance. Given the potential for a widely circulating influenza virus with resistance to all NAIs, new and more effective antivirals, as well as tests to rapidly detect resistant viruses, are needed. Antivirals with different mechanisms of action than NAIs not only would treat NAI-resistant viruses but would also allow combination therapy of susceptible influenza virus infection. However, ensuring access to early antiviral treatment may be challenging: spot shortages of NAIs were reported this past winter in the United States. Because clinical benefit is greatest when NAI treatment is started soon after illness onset, sufficient supplies of antivirals must be available for immediate large-scale distribution in severe pandemics. To facilitate early treatment and help mitigate patient surge at emergency departments and clinics, distribution may require strategies such as fever clinics, nurse telephone triage consultation; and antiviral provision in pharmacies, schools, or other community settings. Efforts to educate clinicians and the public about the clinical

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

benefit of early antiviral treatment are vital, including those at high risk of influenza complications.

Although current understanding of influenza virus pathogenesis has advanced considerably since 1918, challenges remain in developing effective therapies for hospitalized patients with influenza, including those with severe complications. Influenza virus infection of the respiratory tract can trigger a dysregulated cytokine response, resulting in inflammatory tissue damage and increased alveolar capillary permeability; therefore, the potential of adjunctive therapies targeting the host response, including immunomodulators and anti-inflammatory agents, has garnered attention. Immunotherapies for hospitalized influenza patients are in development, but demonstrating clinical benefit of these virus-targeted treatments in severe disease may be challenging without substantial reduction or blockade of the host inflammatory response. The use of systemic corticosteroids, particularly high doses for severely ill patients, has been associated with prolonged shedding of influenza virus and increased risk of ventilator-associated pneumonia, without survival benefit and no data from RCTs involving patients with influenza are available.

Critical care medicine was still a new specialty during the 1968 influenza A(H3N2) pandemic. The next pandemic in 2009 was no-table for its low overall global mortality and the contributions of advanced organ support and intensive care in the management of critically ill patients with acute respiratory distress syndrome (ARDS), multi organ failure, and sepsis triggered by influenza virus or secondary bacterial infection. However, clinical management of patients with influenza is not standardized, and no RCT data exist specifically from patients with influenza to guide optimal management of critically ill patients. Use of advanced organ support for critically ill patients with influenza (eg, low tidal volume ventilation, prone positioning, neuromuscular blockade, optimal fluid management, and extracorporeal membrane oxygenation [ECMO]) is based on data and principles for management of critical illness primarily due to other causes.[7] Secondary bacterial infection, particularly pneumonia, contributed to critical and fatal illness during the 1918,1957,1968, and 2009 pandemics. Yet issues such as accurate diagnosis of invasive bacterial infection with seasonal influenza, antibiotic choice, timing of treatment de-escalation, and optimal duration of therapy remain unresolved.

During the 2009 influenza A(H1N1) pandemic, a monovalent vaccine became available in the United States only after the second wave had peaked. New technologies to expedite vaccine development and manufacturing are needed to improve the effectiveness of seasonal influenza vaccines, to prepare for the next pandemic virus, and to achieve progress toward universal vaccines that confer broad cross-protection. Despite major advances in patient care since 1918, and even with the development of more effective influenza vaccines and universal vaccines in the future, influenza epidemics and pandemics will continue to cause substantial morbidity and mortality worldwide and may overwhelm clinical care capacity–particularly critical care capacity, especially in resource-constrained settings–without further improvements in influenza prevention and clinical management. Estimated mortality associated with the 2009 influenza A(H1N1) pandemic and recent influenza epidemics was highest in areas of the world with the least capacity for acute and intensive care. Building and strengthening clinical capacity is essential in low-resource and middle-income countries

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

and must incorporate infection prevention and control measures as well as access to critical care.

This year is not only the centennial of the 1918 pandemic, but also marks the 50th anniversary of the 1968 pandemic that introduced influenza A(H3N2) viruses into humans. Influenza A(H3N2) virus strains continue to circulate world-wide and predominated again during the 2017–2018 influenza season in the United States. The severity of the past season once more calls attention to the gaps that persist in the clinical management of patients with seasonal influenza. Ongoing prospective, multiyear, multi country, multiregional clinical research networks can serve as platforms for conducting randomized clinical adaptive trials studying interventions to inform the clinical management of influenza.[8] Some have already been established,[8] but wider global networks are needed to address this global disease. Existing networks should be expanded, new ones established, and most importantly, coordination prioritized. Key questions to address include (1) What is the optimal antiviral treatment (including dosing, duration, and possible combination antiviral treatment) for hospitalized non critically ill and critically ill patients with influenza? (2) What antibiotic regimens and durations of treatment are optimal for patients with influenza pneumonia and secondary bacterial infection? (3) What is the role and efficacy of immunomodulating therapy (including optimal dosing, timing of initiation, and duration) for hospitalized non critically ill and critically ill patients with influenza? (4) What advanced organ support strategies (eg, prone positioning, ECMO, conservative vs liberal fluid management) improve outcomes for patients with influenza-related critical illness? (5) Can biomarkers accurately predict development of severe disease in patients with influenza?

Advances in the clinical management of patients with seasonal influenza during annual epidemics will also prepare clinicians to respond better to the next influenza pandemic, whenever that may be.

REFERENCES

1. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults. Lancet. 2015;385(9979):1729–1737 [PubMed: 25640810]
2. Malosh RE, Martin ET, Heikkinen T, et al. Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials. Clin Infect Dis. 2018; 66(10):1492–1500. [PubMed: 29186364]
3. Venkatesan S, Myles PR, Leonardi-Bee J, et al. Impact of outpatient neuraminidase inhibitor treatment in patients infected with iinfluenza A(H1N1)pdm09 at high risk of hospitalization: an individual participant data metaanalysis. Clin Infect Dis. 2017;64(10):1328–1334. [PubMed: 28199524]
4. Ison MG, de Jong MD, Gilligan KJ, et al. End points for testing influenza antiviral treatments for patients at high risk of severe and life-threatening disease. JInfectDis. 2010;201(11):1654–1662.
5. Muthuri SG, Venkatesan S, Myles PR, et al.; PRIDE Consortium Investigators. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection. Lancet Respir Med. 2014;2(5):395–404. [PubMed: 24815805]
6. Hurt AC, Kelly H. Debate regarding oseltamivir use for seasonal and pandemic influenza. Emerg InfectDis. 2016;22(6):949–955.
7. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA. 2018;319(7):698–710. [PubMed: 29466596]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

8. Webb SA, Nichol AD. Bending the pandemic curve: improving decision-making with clinical research. Crit Care Med. 2018;46(3):442–446. [PubMed: 29474325]