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# Preparing intensive care for the next pandemic influenza

Taylor Kain[1] and Robert Fowler[1,2*]

## Abstract

Few viruses have shaped the course of human history more than influenza viruses. A century since the 1918–1919 Spanish influenza pandemic—the largest and deadliest influenza pandemic in recorded history—we have learned much about pandemic influenza and the origins of antigenic drift among influenza A viruses. Despite this knowledge, we remain largely underprepared for when the next major pandemic occurs.

While emergency departments are likely to care for the first cases of pandemic influenza, intensive care units (ICUs) will certainly see the sickest and will likely have the most complex issues regarding resource allocation. Intensivists must therefore be prepared for the next pandemic influenza virus. Preparation requires multiple steps, including careful surveillance for new pandemics, a scalable response system to respond to surge capacity, vaccine production mechanisms, coordinated communication strategies, and stream-lined research plans for timely initiation during a pandemic. Conservative models of a large-scale influenza pandemic predict more than 170% utilization of ICU-level resources. When faced with pandemic influenza, ICUs must have a strategy for resource allocation as strain increases on the system.

There are several current threats, including avian influenza A(H5N1) and A(H7N9) viruses. As humans continue to live in closer proximity to each other, travel more extensively, and interact with greater numbers of birds and livestock, the risk of emergence of the next pandemic influenza virus mounts. Now is the time to prepare and coordinate local, national, and global efforts.

**Keywords:** Influenza, Pandemic, Intensive care, Preparation, Resource allocation, Highly pathogenic avian influenza, Human, Health care worker safety, Triage, Research

## Background

In this literature review, we aim to summarize current knowledge of preparation and potential management for a pandemic influenza virus. With increasing travel, immigration, crowding, and human interaction with livestock, there is an ever-increasing risk of another pandemic. We specifically focus on how intensive care units (ICUs) and their staff may prepare for such an event.

Seasonal influenza has had a long history with humans, but at several points in history, a novel strain of influenza will emerge and lead to a pandemic. A pandemic is an epidemic of disease that has spread across a large region, or even worldwide. There have been four influenza pandemics in the past century, and the circumstances of their emergence are described in this paper.

We outline major steps to prepare for a pandemic including (1) surveillance for new pandemics, (2) building a scalable system to respond to surge, (3) the mass production of vaccines, (4) integrated and coordinated communication, and (5) harmonized research and ethics proposals for rapid initiation. A serious influenza pandemic is very likely to overwhelm the health care system. We describe triage strategies and approaches when resources are limited.

## History and pathogenesis of pandemic influenza

There may be no virus that has shaped human history and mortality more than influenza. We now mark the hundredth anniversary of the deadliest influenza outbreak recorded—the 1918–1919 "Spanish influenza"—which claimed an estimated 50 million lives [1]. Since

* Correspondence: rob.fowler@sunnybrook.ca
[1]Department of Critical Care, University of Toronto, Toronto, ON, Canada
[2]Sunnybrook Health Sciences Centre, Room D478, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada

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the Spanish influenza, pandemics have become an increasing threat with more frequent movement of people and pathogens (Fig. 1).

Pandemic influenza arises distinctly from seasonal influenza. Seasonal viruses circulate globally and evolve due to point mutations in the genetic sequence resulting in small changes in two surface glycoproteins—hemagglutinin (H) and neuraminidase (N). Both influenza A and B undergo this process, known as antigenic *drift*, leading to a recommendation for yearly influenza vaccination [2]. Due to its segmented genome, influenza A also has the unique ability to undergo more significant rearrangements, known as antigenic *shifts*. Antigenic shifts are necessary, but not sufficient, for pandemic influenza to occur, and they usually result in new circulating strains of seasonal influenza viruses. Only influenza A virus is known to have caused pandemics. Influenza C can be a cause of acute respiratory disease in children, but rarely in adults [3]. Studying the development of the four major influenza pandemics of the last hundred years—in 1918–1919, 1957–1958, 1968–1969, and 2009–2010—provides insights into how pandemic influenza may next occur.

The origin of the 1918 "Spanish influenza" remains controversial. Before the genome was decoded by Taubenberger et al. [4], the virus was considered to be derived directly from avian origin [5, 6]. With available genetic information, phylogenetic analysis showed the 1918 pandemic strain contained more similarities with mammalian lineages, either swine or seasonal human H1N1 virus. While debate exists, Smith et al. further showed the 1918 strain resulted from reassortment of genes of circulating swine and human influenza viruses with introduced avian viruses over several years, rather than direct adaptation of an entire avian virus [7]. Regardless of exact etiology, the 1918 pandemic influenza caused devastation in a world still struggling from the Great War. Crowding—of soldiers and civilians—affected the spread of influenza and severity of the illness [ 8, 9]. These crowded conditions provided ideal conditions for a novel influenza strain to become a pandemic, which spread globally as soldiers returned home at the end of the war [10].

It was four more decades before the world faced another two influenza pandemics in short succession. The 1957 and 1968 pandemic viruses formed from genetic reassortment. The 1957 "Asian influenza" H2N2 virus

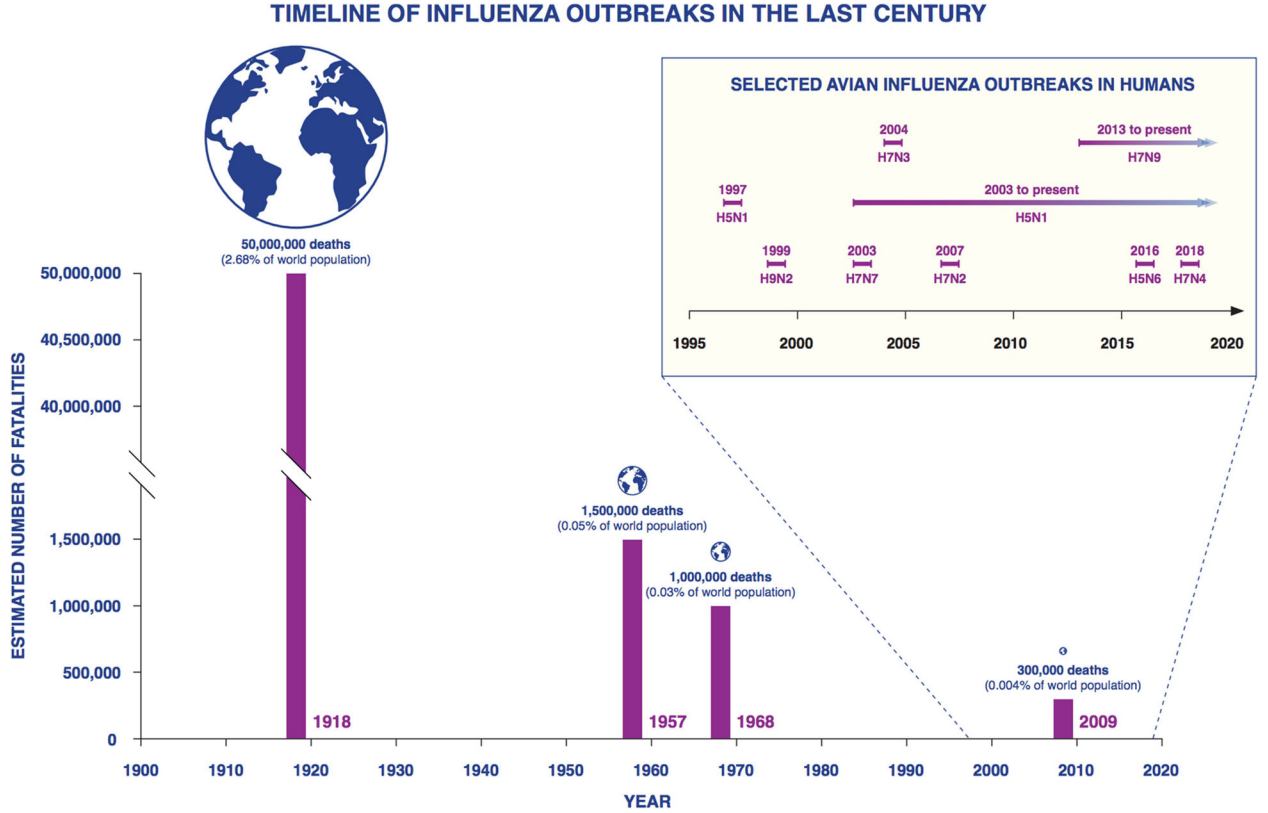


**Fig. 1** Timeline of recorded influenza outbreaks in the past century as well as selected avian influenza outbreaks in humans. In the main figure, globe size corresponds to the estimated number of fatalities relative to global population size at the time, with vertical bars representing the estimated absolute number of fatalities. Numbers are averages from various approximations. In inset, horizontal bars represent time frame that cases from the influenza A virus strain were recorded

resulted from reassortment between low-pathogenic avian influenza (LPAI) H2N2 and seasonal H1N1 virus, while the 1968 "Hong Kong influenza" H3N2 virus resulted from rearrangement of LPAI H3N2 and the seasonal H2N2 virus circulating since the 1957 pandemic [11, 12]. The 1957 "Asian influenza" pandemic caused an estimated 1.1 million excess deaths due to respiratory disease—two thirds in individuals under 65 years old [13]. The 1968 pandemic killed an estimated 1 million individuals [14]. These estimates also under account for mortality in resource poor settings which have less capacity for microbiological testing and documentation.

In March and April 2009, the first pandemic influenza virus of the twenty-first century began to circulate in Mexico and the USA. H1N1pdm09 virus was a novel influenza virus strain in humans. The virus was a combination of Eurasian and North American swine lineages. The majority of the genes were derived from H3N2 and H1N2 triple reassortment viruses in pigs, while their neuraminidase genes were derived from a wholly avian influenza virus that entered the Eurasian swine population [15]. The resulting "swine flu" was distinct from circulating seasonal influenza A viruses, and younger individuals had little or no natural immunity. Mortality globally was estimated between 151,700 and 575,400 in the first year of circulation. Eighty percent of H1N1pdm09-related deaths were in individuals under 65 years, compared to 10–30% in seasonal influenza outbreaks [16].

We have seen pandemic influenza occur multiple times before, and at increasing rates. History has shown us how devastating pandemic influenza can be, especially to younger, healthier individuals. There appears to be an increasing number of pandemics, which is only likely to worsen with growing human population, crowding, and immigration. When considering preparation for the next pandemic, it is not a matter of if it will occur, but rather a matter of when.

## Preparation for a pandemic

Despite attempts at planning, we remain unprepared. Following the 2009 pandemic, the International Health Regulations committee concluded that "the world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained, and threatening public-health emergency" [17]. If we are unprepared to deal with pandemic influenza in developed nations, this pales in comparison with developing nations. By almost all accounts, "Sub-Saharan African plans are not ready to prevent or reduce the death count from [pandemic] influenza" [18, 19]. Intensive care unit (ICU) mortality during the 2009 pandemic varied substantially not only with patient characteristics but also based on region and economic status of the outbreak location; the highest mortality experienced was in South Asia and sub-Saharan Africa [20]. If we are to better prepare for pandemic influenza, it will require multiple components:

1. *Careful surveillance to recognize and mitigate new pandemics*—Controlling pandemics requires early recognition to curb the spread of novel viruses; this necessitates a coordinated surveillance and reporting system. Following the 2009 pandemic, the WHO attempted to mitigate shortcomings by adopting the Pandemic Influenza Preparedness Framework [21], which created sentinel sites for seasonal influenza and to monitor for unusual events that may herald novel influenza. While most surveillance occurs outside of ICUs, with non-critically ill patients, intensivists can still perform a vital function in surveillance of severe disease. In 2009, we saw that our previous reporting systems were not dependable; they relied on patients presenting to physicians, which is influenced by public alarm among other factors. Initial case fatality rates for H1N1 differed by up to 50-fold [22]. Conversely, ICU admission criteria are relatively fixed over time. Cases and deaths can be easily tracked, making ICUs ideal places for surveillance of severe pandemic influenza. To use this strategy, it will be important that intensivists understand the size of their catchment (or referral) area so that they can accurately estimate the local incidence. The creation of early warning systems was one of the main goals of the International Forum for Acute Care Trialists (InFACT) and ongoing efforts such as the SPRINT SARI study [23].
2. *An efficient and scalable emergency response system that can respond to surge capacity*—Pandemic preparedness relies on a system that can surge in times of crisis. Surge capacity has four key components: equipment, physical space, human resources, and system [24]. In pandemics, the duration, scope, and magnitude of the response required are uncertain. In most countries, health care systems operate at or above maximally designed capacity. Many hospitals just do not have sufficient pre-existing resources to respond to surge capacity in an outbreak [25]. Unlike with natural disasters, where the greatest need for resources often occurs early in the time course, pandemic resource requirements will build over months. Outbreaks that become pandemics generally do not take hold in multiple locations at exactly the same time—they are geographically and temporally patchy. Still enough must be immediately available to allow time for other regions and/or manufacturers to meet the increased demand.

Estimates of capacity required in a severe pandemic vary widely. Using the "Flu Surge" model [26] and assuming 35% attack rate over 6 weeks, in Canada's most populous province, Ontario, it is predicted that influenza patient admissions would peak at 1823 per day, which is 72% of all hospital capacity just for influenza patients alone. Demand for ICU resources would peak at 171% of current ICU bed capacity, and ventilator use would peak at 118% capacity. These numbers would only add to the region's current day-to-day ICU utilization rates, which are approximately 90% capacity [27]. In Canada, this would definitely overwhelm current ICU resources. During the 2009 pandemic, in Canada, there were only 3170 ICU beds and 4982 ventilators—a median of 10 ICU beds capable of providing invasive ventilation and 15 ventilators per 100,000 persons [28]. Therapies to treat the most severely affected patients were available in a minority of centers—inhaled nitric oxide in 79 (27.6%) and extracorporeal membrane oxygenation (ECMO) in 39 (13.6%). The uncertainty in scope however leads to uncertain estimates. Models often provide no more accurate estimate of need than expert consensus [29]. In a systematic review of disaster surge capacity, most studies classified an increase in surge capacity of 15–35% as "acceptable," [25] likely far short of what would be required, and certainly short of the *CHEST* consensus statement recommendations of 200% [30]. These estimates also do not account for loss of capacity due to health care worker illness, which we know from previous pandemics and outbreaks can be significant [31].

Even in most well-developed countries, ICU beds are often close to capacity, and it is likely that in a severe influenza pandemic many patients who require a ventilator may not have access to one. Severe acute respiratory distress syndrome (SARS) gave a small-scale example of this. SARS resulted in 8096 cases globally, with only 251 in Canada [32]. Despite this, resources were critically stretched. In Ontario, every negative pressure room in the province was occupied with more patients awaiting at home during the height of the pandemic [33]. ICUs should expand into other areas in a tiered method to facilitate increased demand, with appropriate training of new staff occurring rapidly during times of surge. Intensivists must advocate, and lead, a proactive response with our health care bodies in planning and budgeting for potential surges.

3. *The ability to efficiently and quickly mass produce and distribute vaccines*—Vaccination readiness remains a mainstay of preparation for pandemic influenza, but relies mainly on the efforts of influenza researchers and public health authorities. Details of this are discussed in other reviews [34–36]; briefly, once pandemic influenza is recognized, production of a vaccine will begin. Meanwhile, a priming dose can be considered if stockpiled in specific countries. Once candidate pandemic vaccines are produced, observational studies and clinical trials for safety and efficacy should ideally occur before or alongside their introduction to the clinical setting. This process is inherently long, and measures to streamline the process are vital.
4. *Integrated and coordinated communication*—Excellent communication is vital to a timely response to a disaster scenario. Hospitals and hospital networks should appoint local leads and teams that will respond and coordinate during a pandemic. There should also be secure online directories of all key partners' contact information and clinical and administrative positions. Teams should meet regularly to sharpen communication and build trust, with annual inter-outbreak meetings being the minimum recommended to develop effective relationships [30]. We have seen on a much smaller scale this work with local trauma networks. Hospitals regularly run disaster scenarios, yet these rarely extend beyond the first few hours of an emergency. Broader scenario training or simulation of pandemics is vital to preparedness.
5. *Coordinated research plans with pre-approved research ethics to allow timely initiation*—A well-structured research program is paramount to learn and adapt as pandemic influenza develops. Research during a pandemic must be partially predetermined, have accelerated research ethics vetting, and be pragmatic. Recent pandemics have been characterized by an inability to efficiently undertake interventional trials necessary to guide best practices [37]. The first clinical research step during a pandemic will be descriptive using pre-existing case report forms and formulating an accepted case definition [38]. Most large jurisdictions already have pre-approved tiered case report forms, with minimal or expanded versions, so they may serve as data collection tools for clinical trials [39]. Funding agencies must also provide shortened intervals from application to approval, ideally with prepositioned funds for immediate vetting and release. Finally, there should be coordinated communication of research interests and intent across global regions at the outset to promote complementary and generalizable results without unnecessary duplication in efforts [40].

## Intensive care and hospital management during a pandemic

While emergency departments are likely to encounter the first patients with pandemic influenza, many sick patients

should be cared for by intensivists, so they are critical to guiding triage when demand exceeds capacity. Intensivists therefore should be part of strategic planning committees before, during, and after pandemics, to coordinate ICU response with hospital and regional efforts for triage, clinical care, and infection control.

During a large-scale pandemic, resources will become limited, even in developed nations. Multiple and context-appropriate strategies will be required to build a sustained surge capacity for mass critical care. While short-term capacity is crucial, long-term sustainability will be more important. The starting point for this in Canada is the Canadian Pandemic Influenza Plan [41]. In the USA, these include, among others, Pandemic Influenza: Preparedness, Response, and Recovery from the Department of Homeland Security [42], and the Pandemic Influenza Plan from the CDC and Department of Health and Human Services [43]. Clinicians must be adaptable when using pre-existing protocols, as they are often based on historical and non-generalizable illness syndromes and outcomes. Resource-limited countries will also need significant adaptation, likely with a greater focus on pre-hospital and transportation systems [44] (Fig. 2).

Treatment of severe influenza involves a combination of specific and supportive therapies. While there is limited evidence of the effectiveness of neuraminidase inhibitors in severe influenza, they are likely to be recommended for use in critically ill patients during the initial phases of pandemic influenza [41–43]. Pandemic influenza should also be treated according to the pathophysiological mechanism of injury. While influenza results mainly in upper and lower respiratory tract infection, secondary bacterial pneumonias, acute respiratory distress syndrome (ARDS), encephalitis, and myocarditis complicate severe illness. Many patients will require mechanical ventilation. If demand outstrips critical care capacity, a triage system will be needed in developed health systems; this already routinely occurs in resource-limited settings. Developing a pandemic-specific and responsive triage system has proven challenging even in highly resourced systems. Triage systems based upon the severity of illness scores, beyond which intensive care might be considered futile, are fraught with poor performance for individual patient decisions and were not developed involving the patients to whom the triage tool would be applied. For example, the 2009 pandemic affected young non-immune patients, many of whom had high illness severity scores; however, with intensive care, mortality was low in developed countries [45]. Modeling data suggests that to perform better than a first-come, first-served basis, the triage tool would have to have a 90% sensitivity and specificity [46]. The Ontario Health Plan for an Influenza Pandemic critical care triage protocol assembled a task force with public consultation to determine the best distribution of resources during a pandemic. Surprisingly, only "first-come, first-serve" and "random selection" principles were favored by the panel, based on a need to balance a utilitarian approach with equity considerations. They suggested that "these criteria serve as a defensible 'fail safe' mechanism for any triage protocol" [45] (Table 1).

Beyond mechanical ventilation, access to extracorporeal life support (e.g., ECMO) will be an even more limited, but perhaps life-saving, resource during a pandemic [47]. There may be barriers to patient transfer between institutions given infection control concerns, limiting access to treatment. Mobile units capable of setting up ECMO at peripheral sites before transfer may be preferable during a pandemic and was a successful approach used during the 2009 H1N1 pandemic [48]. While

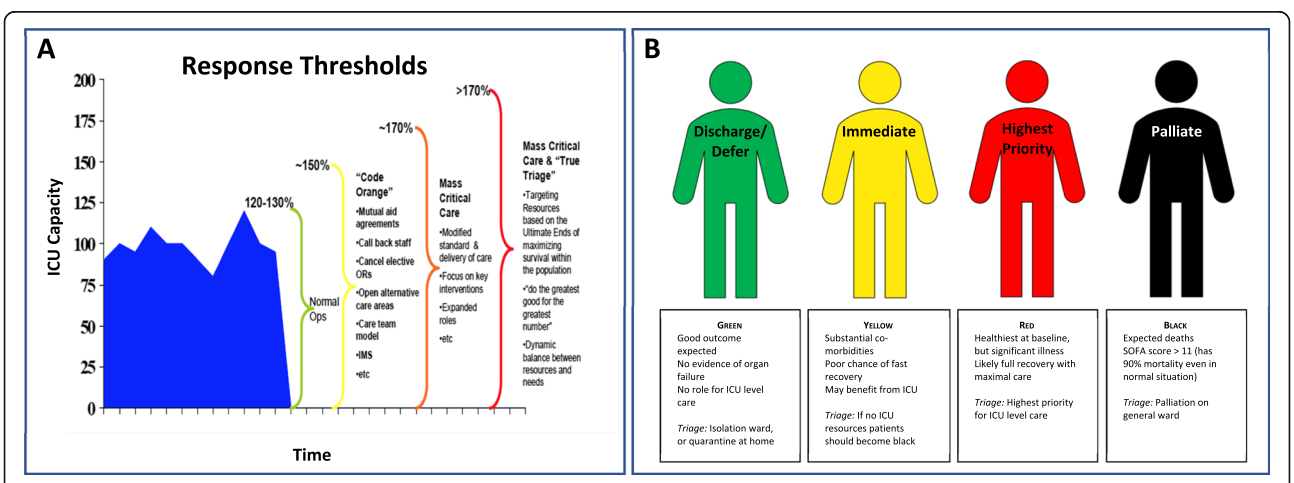


**Fig. 2** **a** Stages of mass critical care, with various ICU response thresholds. As a pandemic progresses, resources become scarce and there is increasing strain placed on the health care system from more cases [24]. **b** A potential triage strategy for various patient groups as the capacity of the ICU is slowly overwhelmed to streamline admissions without the greatest opportunity for benefit from ICU level care. Transparency is paramount in this process

**Table 1** Outline of possible triage strategies during a pandemic or other emergency situation where resources are limited. Multiple task forces favor FCFS and traditional methods as the most ethical during a pandemic

| Method | Mechanism of medical triage | Prioritizing factor | Examples |
|---|---|---|---|
| Traditional | No formal mechanism of triage | No criteria | Many health care systems |
| Barron Dominque-Jean Larry | Treatment of the most urgent (i.e., sickest) patients, and deferring less sick or likely fatal cases | Market pull factor | How current system works in most of the developed world |
| Wilson | Concentrate treatment on the most likely to be successful. Some low probability cases will die that otherwise may have been saved | Likelihood of success | Pragmatic approach |
| First-come, first-served (FCFS) | Treatment based on arrival/ presentation regardless of severity of illness, rank, or any other criteria | Order of arrival | In part, how current system works in most of the world |
| Greatest good for greatest number (GGGN) | Depriving severely ill patients needing large amount of resources and attention, for multiple patients that are less sick and require less resources | Number of patients treated for given resources | Utilitarian approach |
| Less severity first treatment (LSFT) | Prioritize healthier patients that can be treated quickly to allow them to return to society, the labor force, etc. | Patients who are less sick | Many emergency departments have a fast track section |
| Maximize the fighting strength | Treat patients who are most likely to quickly return to duty with the least resource expenditure | Time needed for treatment of patients | Prioritize HCWs, key public health or government jobs, etc. |

ECMO appears to be effective in the treatment of selected patients with severe ARDS [49–51], it relies on a smaller scale pandemic. In the event of a pandemic that overwhelmed the health care system, existing ECMO resources might be allocated using existing locally acceptable criteria, coupled with a first-come, first-served basis, understanding that in a sustained outbreak, time-limited trials of treatment represent one mechanism to effect triage.

During a severe pandemic, context-appropriate standards of care would be required if demand for resources substantially exceeds capacity. Such a crisis-based standard of care might be defined as a "substantial change in usual healthcare operations and the level of care it is possible to deliver, which is made necessary by a pervasive … or catastrophic disaster" [52]. The release of crisis standards of care would be made by the regional or national governments, through Ministries of Health or Public Health Agencies, but intensivists would reasonably be expected to be involved in this process of development. Such standards might consider (1) mechanical ventilation, (2) IV fluid resuscitation, (3) vasopressor administration, (4) sedation and analgesia, (5) antiviral treatment, and (6) therapeutics and interventions, such as renal replacement and nutrition for critically ill patients [29]. Thought should also be placed on dealing with special populations—such as children and pregnant women [30].

While providing high levels of critical care through a pandemic, we must maintain the safety and wellbeing of health care workers (HCWs). Beyond any professional obligation to HCW safety, there is also likely to be a public health benefit to this—when HCWs become sick, or fear becoming sick, they are less able to perform clinical duties. Lessons can be learned from experiences in Toronto and other major centers with SARS. Approximately 20% of cases globally were in HCWs [53]. Nosocomial amplification is a common aspect of many outbreaks. While influenza is regularly spread through contact and droplet transmission, certain procedures in hospitals—intubation, ventilation, and bronchoscopy—create potential airborne transmission. Infection control practices are essential to limiting the spread of pandemic influenza [54]. The loss of clinical personnel to illness resulted in the shutdown of most non-urgent healthcare for the entire city. Preventing this loss of capacity by protecting health care personnel is a critical element of an effective response.

Public health officials working with clinical experts must make rapid recommendations about appropriate personal protective equipment, and for novel threats, these recommendations must be updated as more information about the pandemic becomes available. Pre-pandemic simulations can play a vital role in preparing staff for these outbreaks—for infection prevention and control, for clinical care practices, and also to help staff prepare "emotionally" for stressful environments.

We can also design ICUs to limit the spread of infection. In Singapore, following SARS, the emergency room

was redesigned so that febrile patients were allocated where air flow patterns did not carry to other areas of the department [55]. In Toronto after SARS, the intensive care unit at the main outbreak center was rebuilt with an entire pod of beds that could be converted into a negative pressure ward. These designs and many others will help manage the next outbreak and these factors should be considered when all new hospitals are being constructed. During a pandemic, visitors and non-essential personnel should likely be limited in hospital entry, while respecting the needs of patients and families to safely connect—either in person with appropriately supported PPE or using novel ward design and/or electronically augmented virtual connections.

## Our current landscape

The US Department of Homeland Security "views pandemic influenza as both the most likely and the most lethal of all [infectious] threats facing the United States," [56] a concern shared by many health jurisdictions [57]. Interpandemic periods average 40 years, but we are at an ever-increasing risk for serious pandemics [58]. As humans continue to live in more crowded conditions, travel and migrate more extensively, and continue to farm livestock in proximity to more densely populated areas, the risk for genetic reassortment of influenza A viruses is perhaps higher than ever before.

As outlined above, the most recent pandemic influenza virus, in 2009, originated from pigs. While swine will remain a major concern for further pandemics, birds likely pose the greatest risk for deadly pandemic influenza virus strains. Like pigs, they serve as reservoirs and can be infected with multiple strains making them a potential mixing vessel [59]. There are several strains of high-pathogenic avian influenza (HPAI) that pose the greatest threat to humans [60]. In 1997, Hong Kong reported the first outbreak of influenza A(H5N1) in humans. Virus was transmitted from chickens directly to humans, and 6 of 18 patients died [61]. Since 2003, the virus strain has spread to Europe and Africa killing millions of poultry and causing hundreds of human infections. While there has been no sustained human-to-human transmission of H5N1, the overall mortality rate is close to 60%. In 2013, a novel avian influenza A virus, H7N9, emerged and began to spread across poultry in China. H7N9 has resulted in over 1500 human cases with a 40% mortality rate [58]. Most of those infected in recent outbreaks could reasonably be expected to receive care in an ICU.

Global hot spots for emerging infectious diseases and pandemic influenza are often in some of the regions with the least resources. Many countries where HPAI remains a major pandemic threat have limited participation (data generation, genetic analysis, data share, etc.) in avian influenza surveillance [62]. In addition, some countries may have political, economic, or scientific disincentives to share surveillance data gathered [63].

The 2009 H1N1 pandemic was, by most accounts, not as severe as initially feared. Many have therefore become complacent about the prospect of an influenza pandemic. However, it should be noted that 5 months after the discovery of the novel virus in Mexico, 50% of children in Hong Kong were infected with H1N1, proving rapid dissemination of a pandemic virus [64]. Vaccines cannot be developed in time to protect against the first wave of a novel pandemic and should a deadlier virus, such as HPAI, spread at this rate, the results would reflect those seen in a Hollywood movie. We are unprepared at a local level in ICUs and at a global public health level for such a situation. Now is the time to act in our own hospitals and to use our influence to help guide government policies.

## Conclusions

The threat of a new influenza pandemic remains high. Health care systems, and intensive care units, around the world are at risk of clinical demand outstripping capacity. Action should be taken now to build surveillance systems, a scalable response with focus on vaccine production, effective cross-jurisdictional communication and clinical support, the potential to require fair and effective patient triage systems, in addition to research embedded within a pandemic plan.

### Abbreviations

H: Hemagglutinin; N: Neuraminidase; LPAI: Low-pathogenic avian influenza; HPAI: High-pathogenic avian influenza; ICU: Intensive care unit; SARI: Severe acute respiratory infection; ECMO: Extracorporeal membrane oxygenation; CDC: Centres for Disease Control; ARDS: Acute respiratory distress syndrome; FCFS: First-come, first-served; GGGN: Greatest good for the greatest number; LSFT: Less severe, first treatment; HCW: Health care workers

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### Authors' contributions

TK wrote and compiled the manuscript with input and guidance from RF. RF played a major role in concept and design of the manuscript. RF also edited the manuscript for content, flow, and length. Both authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

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REVIEW Open Access

# Influenza virus-related critical illness: pathophysiology and epidemiology

Andre C. Kalil[1*] and Paul G. Thomas[2]

## Abstract

Influenza virus affects the respiratory tract by direct viral infection or by damage from the immune system response. In humans, the respiratory epithelium is the only site where the hemagglutinin (HA) molecule is effectively cleaved, generating infectious virus particles. Virus transmission occurs through a susceptible individual's contact with aerosols or respiratory fomites from an infected individual. The inability of the lung to perform its primary function of gas exchange can result from multiple mechanisms, including obstruction of the airways, loss of alveolar structure, loss of lung epithelial integrity from direct epithelial cell killing, and degradation of the critical extracellular matrix.
Approximately 30–40% of hospitalized patients with laboratory-confirmed influenza are diagnosed with acute pneumonia. These patients who develop pneumonia are more likely to be < 5 years old, > 65 years old, Caucasian, and nursing home residents; have chronic lung or heart disease and history of smoking, and are immunocompromised.
Influenza can primarily cause severe pneumonia, but it can also present in conjunction with or be followed by a secondary bacterial infection, most commonly by *Staphylococcus aureus* and *Streptococcus pneumoniae*. Influenza is associated with a high predisposition to bacterial sepsis and ARDS. Viral infections presenting concurrently with bacterial pneumonia are now known to occur with a frequency of 30–50% in both adult and pediatric populations. The H3N2 subtype has been associated with unprecedented high levels of intensive care unit (ICU) admission. Influenza A is the predominant viral etiology of acute respiratory distress syndrome (ARDS) in adults. Risk factors independently associated with ARDS are age between 36 and 55 years old, pregnancy, and obesity, while protective factors are female sex, influenza vaccination, and infections with Influenza A (H3N2) or Influenza B viruses.
In the ICU, particularly during the winter season, influenza should be suspected not only in patients with typical symptoms and epidemiology, but also in patients with severe pneumonia, ARDS, sepsis with or without bacterial co-infection, as well as in patients with encephalitis, myocarditis, and rhabdomyolysis.

**Keywords:** Influenza, Epidemiology, Pneumonia, Sepsis, ARDS, Complications

## Background

### The pathophysiology of influenza virus infection

Human influenza virus infection replicates primarily in the respiratory epithelium. Other cell types, including many immune cells, can be infected by the virus and will initiate viral protein production. However, viral replication efficiency varies among cell types, and, in humans, the respiratory epithelium is the only site where the hemagglutinin (HA) molecule is effectively cleaved, generating infectious virus particles. Virus transmission occurs when a susceptible individual comes into contact with aerosols or respiratory fomites from an infected individual [1].

The ferret has traditionally been used as a model of influenza transmission as most human influenza viruses do not need any adaptation to infect and transmit among ferrets. Studies in ferrets have identified the soft palate as a major source of influenza viruses that are transmitted between individuals. Notably, the soft palate is enriched in α2,6-linked sialic acids, which are preferred by the hemagglutinin proteins currently found in circulating human influenza viruses [2]. This enrichment also occurs in the soft palate of humans [3].

The primary mechanism of influenza pathophysiology is a result of lung inflammation and compromise caused by direct viral infection of the respiratory epithelium,

* Correspondence: akalil@unmc.edu
[1]Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE 68198, USA
Full list of author information is available at the end of the article

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combined with the effects of lung inflammation caused by immune responses recruited to handle the spreading virus (Table 1). This inflammation can spread systemically and manifest as a multiorgan failure, but these consequences are generally downstream of lung compromise and severe respiratory distress [4]. Some associations have also been observed between influenza virus infection and cardiac sequelae, including increased risk of myocardial disease in the weeks following influenza virus infection. The mechanisms of this, beyond a general inflammatory profile, are still unresolved [5, 6].

## How influenza triggers ARDS

Influenza virus infects respiratory epithelial cells that line the upper (including nasal) through lower (to the alveoli) respiratory tract. A key parameter in determining the extent of associated disease is the degree to which the lower respiratory tract becomes invaded by the virus [7]. The infection of alveolar epithelial cells in particular appears to drive the development of severe disease, destroying the key mediators of gas exchange and allowing viral exposure to endothelial cells. Early interactions between influenza virus, the alveolar macrophages that are resident in the lung airways, and the epithelial lining are an important determinant for alveolar disease progression [8]. Once this fragile layer is breached, cytokine and viral antigen exposure to the endothelial layer can amplify inflammation, with endothelial cells a major source of pro-inflammatory cytokines that will drive the magnitude and character of subsequent innate and adaptive immune responses [9].

Ultimately, the involvement of significant portions of the airways in an infectious response, either by direct viral infection or by damage from the responding immune system, represents a physiological failure. The inability of the lung to perform its primary function of gas exchange can result from multiple, non-exclusive mechanisms, including obstruction of the airways, loss of alveolar structure, loss of lung epithelial integrity from direct epithelial cell killing, and degradation of the critical extracellular matrix that maintains the structure of the lung [10]. This latter area has been relatively understudied, with the relationship between the immune response and extracellular matrix structure not fully elucidated. Further, the key pathways regulating extracellular matrix degradation and regeneration in the context of infection and in the restoration of healthy lung functioning are not fully understood [11, 12].

Therapies targeting these pathways may have efficacy later in the response, after traditional antivirals have been found to have reduced effects [13]. Towards this end, a report found that inhibition of the collagenase MT1-MMP (MMP14) limited tissue damage and improved survival in a mouse model of severe influenza virus infection and in a model of influenza-pneumococcal coinfection [14]. Targeting the downstream effects of inflammation and immune-associated lung damage may be a viable means of limiting influenza-associated pathology [15].

Other approaches to address the host response directly rather than solely focusing on the virus have included targeting innate immune pathways that amplify inflammatory signals and contribute to epithelial damage. The inflammasome, an innate signaling complex that is required for IL-1β and IL-18 secretion has been implicated in multiple studies as influenza-associated pathology [16, 17]. Suppressing inflammasome activation later in infection, by targeting NLRP3 (a key component of inflammasome signaling) downstream of influenza has had positive effects on recovery in animal models [18, 19]. Following inflammasome activation, secondary cytokine and chemokine signaling can lead to the recruitment of tissue-damaging neutrophil and inflammatory monocyte populations. Experiments blocking CXCR1/2 signaling, a key receptor pathway necessary for neutrophil recruitment to the site of inflammation showed protection in murine infections with influenza, *Staphylococcus pneumoniae*, or combined infections. Given the prominence of secondary bacterial infections (discussed in detail below) in influenza-associated disease, such host-directed therapies may have significant clinical utility [20]. Neutrophils can mediate tissue damage by secreting high levels of tissue remodeling enzymes such as MMPs, but also amplify inflammation by secreting extracellular traps (NETs). In mouse models, NETs were highly correlated with acute lung injury, which could be exacerbated by shifting cellular infiltrates in favor of neutrophils by depleting macrophages [21]. Similar NET structures have been observed in humans suffering from severe influenza disease. In one study of severe H7N9 and H1N1pdm09 virus infection, levels of NETs at admission were correlated with clinical scores (APACHE II) [22].

**Table 1** Host and viral mechanisms of influenza-associated pathogenesis

| Host and viral mechanisms of influenza-associated pathology | | |
|---|---|---|
| Direct viral induced pathology | Innate immune responses | Adaptive immune responses |
| • Epithelial cell death (apoptosis and necrosis)<br>• Alveolar compromise<br>• Denudation of the airways | • Local and systemic cytokine production<br>• Innate immune cellular infiltration (neutrophils, inflammatory monocytes)<br>• Extracellular matrix degradation | • Exuberant T cell responses (CD4 and CD8)<br>• Excess cytokine production<br>• Immune-cell mediated epithelial denudation<br>• Amplification of inflammation and local and systemic cytokine production |

Targeting host inflammation has been of increasing interest for the development of new therapeutics for severe influenza. One study used the well-characterized mTOR inhibitor rapamycin/sirolimus to suppress inflammation, leading to improved outcomes, correlated with reduced inflammasome activity [23, 24]. Targeting the mTOR pathway as a means to reduce inflammation and promote recovery implicates host metabolism in the etiology of severe influenza disease, given the central role mTOR plays in nutrient sensing. Metabolic disruptions have been noted in local and systemic analyses of severe cases of influenza [25] and metabolic interventions have been shown to alter host response profiles in ways that could be protective or harmful depending on the infection context. For example, in mouse models of bacterial sepsis or influenza virus infection, glucose restriction had opposing effects, protecting against bacterial sepsis but exacerbating influenza-associated disease [26]. The role of metabolism in modulating viral infection is complex, as while the host needs particular nutrients to support its immune activities, the virus itself requires significant host cell metabolic resources to maintain its replication, including glucose and glutamine [27, 28]. Targeting these viral metabolic requirements may open additional therapeutic windows. Additionally, the global metabolic state within a host has been shown to have profound effects on the course of viral infection and the progression to ARDS-phenotypes. Obese animals and humans are significantly more susceptible to severe influenza, with increase in lung injury and sustained viral replication, indicative of failures of host immunity and potentially increased viral pathogenesis. The mechanisms relating to obesity to susceptibility are likely complex and multi-factorial, including increased inflammation and decreased wound healing in obese individuals. Additionally, obesity dampens some features of adaptive immunity that may delay viral clearance or increase susceptibility to initial infection [29–31].

### Influenza clinical progression to pneumonia and ARDS

Approximately 30–40% of the hospitalized patients with laboratory-confirmed influenza are diagnosed with acute pneumonia. These patients who develop pneumonia are more likely to be young (< 5 years old), old (> 65 years old), Caucasian, and nursing home residents; have chronic lung or heart disease and history of smoking; and are more commonly immunocompromised. Of note, pregnant women, extreme obesity, Native Americans, and Alaska natives are also more prone to develop severe Influenza complications [32–35]. Nonetheless, unlike seasonal epidemics of influenza virus infection that display these classic risk factors, pandemics such as the 2009 H1N1 were associated with a higher rate of hospitalized respiratory failure in previously healthy and young adults [36, 37]. More recently, a large cohort from Australia and New Zealand reported that during the winter of 2017, the predominant H3N2 virus strain was associated with unprecedented high levels of ICU admission due to viral and bacterial pneumonias, even higher than 2009 H1N1 pandemic [38].

There are no reliable statistics on the actual incidence or prevalence of influenza-related ARDS in either pediatric or adult populations. However, it is known that the vast majority of ARDS is caused by bacterial sepsis and non-infectious etiologies such as trauma, pancreatitis, smoke inhalation, and drug toxicity [39, 40]. Observational studies suggest that within the small proportion of viral-induced ARDS in the pediatric population, most are caused by respiratory syncytial virus and Influenza A, while Influenza A is the predominant viral etiology of ARDS in the adult population [41, 42]. A European cohort from the Eurosurveillance showed that the risk factors independently associated with ARDS in patients diagnosed with influenza are age between 36 and 55 years old, pregnancy, and obesity, while protective factors associated with ARDS were female sex, influenza vaccination, and infections with Influenza A (H3N2) or Influenza B viruses. Notably, the only factors that remained significantly associated with death were increasing severity score and age greater than 55 years old [41]. In another cohort from China, it appears that viral strain was a significant factor, as, compared to H1N1, ARDS caused by H7N9 was associated with higher disease severity, higher rates of mechanical complications and hospital-acquired pneumonias, and increased mortality [42]. A potential new risk factor for the development of ARDS during the influenza season is the performance of cardiac surgery [43].

The challenge of diagnosing pneumonia and ARDS in patients with positive laboratory results for influenza relates to the temporality of the clinical events. Influenza virus infection alone can cause severe pneumonia and ARDS, but it can also act in conjunction with a bacterial infection (discussed below). It can precede a pneumonia episode caused by a secondary bacterial infection, most commonly by *S. aureus* and *S. pneumoniae*, or can be followed by an episode of nosocomial pneumonia [44]. Clinicians commonly fail to clinically diagnose influenza in up to two-thirds of patients whom have confirmed influenza virus infection [45]. In the case of severe pneumonia or ARDS, the only reliable clue that influenza is a possible causal agent is the presentation during the peak season of the epidemic because the symptomatology alone cannot distinguish severe influenza from other viral or bacterial respiratory infections. Primary influenza pneumonia shows persistence and/or subsequent worsening of respiratory symptoms, while secondary bacterial pneumonia occurs 1–3 weeks as a "relapse" after the initial Influenza

symptoms have ended or subsided; however, bacterial co-infection can also occur a few days after the Influenza illness onset. That said, only 5% of all severe pneumonias admitted to the ICU are from a viral etiology [46].

### Influenza presenting as sepsis

The immune response to influenza shares many common pathways with the response to bacteria, thus it should not be surprising that an influenza virus infection can have a very similar clinical presentation to bacterial sepsis [9, 47, 48]. Specifically, several studies have demonstrated that both Toll-like receptors 2 and 4, which are the main receptors for Gram-positive and Gram-negative bacteria, are also related to influenza pathogenicity [49–51]. The inflammatory response also varies according to the viral strain; for example, H5N1 virus produces a stronger response than H1N1pdm09 virus and H7N7 in blood macrophages, but H1N1pdm09 produces a more robust cytokine production than other strains [52–54]. In addition, similar to bacterial sepsis, endothelial damage and microvascular permeability changes leading to tissue edema and organ failure have been observed with influenza virus infections [55, 56]. Analogous to the influenza virus predisposition to secondary bacterial pneumonia, influenza virus increases by 6-fold the progression to secondary bacterial sepsis [57]. Adults with severe influenza-induced organ failure and pediatric patients with high PIM scores and acute renal failure have a greater risk of mortality [58–60]. A large multinational cohort evaluating the causes of sepsis in approximately 1600 patients from Southeast Asia found that 4% of all sepsis were caused by influenza viruses [61]. In the recent 2017 winter season with the predominant H3N2 virus strain, an Australasian study reported that the ICU admission for sepsis was much higher than expected, which the authors attributed in part to the influenza virus season [38].

### Role of viral-bacterial co-infections and their effect on outcomes

The occurrence of viral-bacterial respiratory co-infections has been described for over a century, including the period of the 1918 influenza pandemic; however, until just a few years ago, the general evidence pointed to this as a uncommon event without major changes on patients' outcomes. The recent advent of more rapid and available microbiological diagnostic tests (e.g. real-time reverse-transcriptase polymerase chain reaction) has revealed a very different picture. Nowadays viral etiologies per se are responsible for one-third of all cases of community-acquired pneumonias (CAP) [62, 63]. These etiologies include influenza, parainfluenza, coronavirus, rhinovirus, metapneumovirus, adenovirus, respiratory syncytial virus, and other less frequent microorganisms. Viral infections presenting concurrently with bacterial CAP are now known to occur with a frequency of 30–50% in both adult and pediatric populations [64–67]. Interestingly, it would be more intuitive to assume that CAP would be the most severe manifestation of these co-infections, but more recently there have been several studies demonstrating these viral-bacterial infections also affect 10–20% of patients with hospital-acquired pneumonia (HAP) [44, 68–70]. In a large cohort study with over 2,000 patients hospitalized with severe H1N1pdm09 influenza, the following risk factors were identified for developing HAP: need for mechanical ventilation, sepsis, ICU admission on the first day, lymphocytopenia, older age, and anemia. Of note, growing evidence suggests that 20–30% of pediatric and adult patients presenting with suspected bacterial sepsis may have a viral co-infection (e.g. influenza, metapneumovirus, coronavirus, and respiratory syncytial virus) and about two thirds of these cases are commonly missed by clinicians [38, 71, 72]. Current data still lacks proof that the clinical presentation with viral-bacterial co-infections directly leads to worse outcomes, but a growing body of evidence suggests that influenza-bacterial co-infections are associated with higher morbidity and higher mortality [65, 73–76]. In fact, a recent study showed that the presence of co-infection in adults with influenza-associated acute respiratory syndrome requiring extra-corporeal membrane oxygenation was significantly associated with a fourfold increase in mortality [77], and another study in children with *Staphylococcus aureus* co-infection with influenza-related critical illness also showed a ninefold significant increase in mortality [78].

The mechanism of increased susceptibility to bacterial co-infection after an influenza virus infection has been a focus of many studies. The lung immune environment is substantially altered after influenza virus infection, with early depletion of alveolar macrophages [79]. As these cells play a key role in the response to many bacterial infections, their loss may play a critical part in increasing susceptibility. Additionally, the normal regulatory mechanisms that are induced by any inflammatory response are triggered by a viral infection. These include the up-regulation of key negative regulators on the surface of lung immune cells, including CD200 on airway macrophages. Such suppressor activity is necessary to allow tissue repair and avoid pathological consequences of overzealous immune responses, but they can allow a window of opportunity for bacteria [80]. Similarly, influenza virus infection induces systemic glucocorticoids that can dampen inflammation to protect tissue integrity, but allow increased bacterial growth, as was shown in a mouse model of influenza virus-*Listeria* co-infection [81]. Blocking the glucocorticoid response actually led to death from the inflammation associated with the influenza virus infection, demonstrating the balance between tolerance and pathogen resistance that can be difficult to determine in the co-infected host [81].

### Other less common severe complications of Influenza

Acute myositis accompanied by rhabdomyolysis may rarely happen, most commonly in children who present with extreme tenderness of lower extremities, and the laboratory investigation shows marked elevation of serum creatinine phosphokinase and myoglobinuria [82]. Myocarditis and pericarditis have also been rarely described in clinical cases, but demonstrated in autopsy studies [83, 84]. Central nervous system complications associated with influenza include encephalitis, acute disseminated encephalomyelitis, transverse myelitis, aseptic meningitis, and Guillain-Barre syndrome [85–87] (Table 2).

## Conclusions

Influenza virus affects the respiratory tract by direct viral infection or by damage from the immune system response. In humans, the respiratory epithelium is the only site where the hemagglutinin (HA) molecule is effectively cleaved, generating infectious virus particles. Virus transmission occurs through contact with aerosols or respiratory fomites from an infected individual. The inability of the lung to perform its primary function of gas exchange can result from multiple mechanisms, including obstruction of the airways, loss of alveolar structure, loss of lung epithelial integrity from direct epithelial cell killing, and degradation of the critical extracellular matrix.

Approximately 30–40% of hospitalized patients with laboratory-confirmed influenza are diagnosed with acute pneumonia. These patients who develop pneumonia are more likely to be < 5 years old, > 65 years old, Caucasian, and nursing home residents; have chronic lung or heart disease and history of smoking; and are immunocompromised.

Influenza can primarily cause severe pneumonia, but it can also present in conjunction with or be followed by a secondary bacterial infection, most commonly by *S. aureus* and *S. pneumoniae*. Influenza is associated with a higher predisposition to bacterial sepsis and ARDS. Viral infections presenting concurrently with bacterial pneumonia are now known to occur with a frequency of 30–50% in both adult and pediatric populations. Influenza A (H3N2) virus has been associated with unprecedented high levels of intensive care unit (ICU) admission.

Influenza A virus is the predominant viral etiology of acute respiratory distress syndrome (ARDS) in adults. Risk factors independently associated with ARDS are age between 36 and 55 years old, pregnancy, and obesity, while protective factors are female sex, influenza vaccination, and infections with Influenza A (H3N2) or Influenza B viruses.

In the ICU, particularly during the winter season, Influenza should be suspected not only in patients with typical symptoms and epidemiology, but also in patients with severe pneumonia, ARDS, sepsis with or without bacterial co-infection, as well as in patients with encephalitis, myocarditis, and rhabdomyolysis.

**Table 2** Severe influenza complications

| Severe influenza complications |
|---|
| Influenza pneumonia |
| Secondary bacterial pneumonia |
| ARDS |
| Influenza sepsis |
| Secondary bacterial sepsis |
| Myositis and rhabdomyolysis |
| Acute myocarditis |
| Acute pericarditis |
| Acute encephalitis |
| Acute disseminated encephalomyelitis |
| Transverse myelitis |
| Aseptic meningitis |
| Guillain-Barre syndrome |

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None.

#### Summary figure

- Influenza virus affects the respiratory tract by direct viral infection or by damage from the immune system response.
- Approximately 30–40% of hospitalized patients with laboratory-confirmed influenza are diagnosed with acute pneumonia.
- Coinfections with other viruses and bacteria are common.
- Influenza should be suspected not only in patients with typical symptoms and epidemiology, but also in patients with severe pneumonia, ARDS, sepsis, encephalitis, myocarditis, and rhabdomyolysis.

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#### Author details
[1]Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE 68198, USA. [2]Immunology Department, St. Jude Children's Research Hospital, Memphis, TN, USA.

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REVIEW Open Access

# Influenza virus-related critical illness: prevention, diagnosis, treatment

Eric J. Chow[1,2], Joshua D. Doyle[1,2] and Timothy M. Uyeki[2*]

## Abstract

Annual seasonal influenza epidemics of variable severity result in significant morbidity and mortality in the United States (U.S.) and worldwide. In temperate climate countries, including the U.S., influenza activity peaks during the winter months. Annual influenza vaccination is recommended for all persons in the U.S. aged 6 months and older, and among those at increased risk for influenza-related complications in other parts of the world (e.g. young children, elderly). Observational studies have reported effectiveness of influenza vaccination to reduce the risks of severe disease requiring hospitalization, intensive care unit admission, and death. A diagnosis of influenza should be considered in critically ill patients admitted with complications such as exacerbation of underlying chronic comorbidities, community-acquired pneumonia, and respiratory failure during influenza season. Molecular tests are recommended for influenza testing of respiratory specimens in hospitalized patients. Antigen detection assays are not recommended in critically ill patients because of lower sensitivity; negative results of these tests should not be used to make clinical decisions, and respiratory specimens should be tested for influenza by molecular assays. Because critically ill patients with lower respiratory tract disease may have cleared influenza virus in the upper respiratory tract, but have prolonged influenza viral replication in the lower respiratory tract, an endotracheal aspirate (preferentially) or bronchoalveolar lavage fluid specimen (if collected for other diagnostic purposes) should be tested by molecular assay for detection of influenza viruses.

Observational studies have reported that antiviral treatment of critically ill adult influenza patients with a neuraminidase inhibitor is associated with survival benefit. Since earlier initiation of antiviral treatment is associated with the greatest clinical benefit, standard-dose oseltamivir (75 mg twice daily in adults) for enteric administration is recommended as soon as possible as it is well absorbed in critically ill patients. Based upon observational data that suggest harms, adjunctive corticosteroid treatment is currently not recommended for children or adults hospitalized with influenza, including critically ill patients, unless clinically indicated for another reason, such as treatment of asthma or COPD exacerbation, or septic shock. A number of pharmaceutical agents are in development for treatment of severe influenza.

**Keywords:** Influenza, Influenza vaccination, Influenza testing, Antiviral treatment

## Background

Annual seasonal influenza epidemics of variable severity result in significant morbidity and mortality in the United States (U.S.) and worldwide [1–3]. In temperate climate countries, including the U.S., influenza activity peaks during the winter months whereas in tropical regions influenza activity may be more variable [4–6]. Most persons with symptomatic influenza virus infection have self-limited uncomplicated upper respiratory tract illness. One study estimated that during 2010–2016, approximately 8.3% of the U.S. population experienced symptomatic influenza each year [7]. However, complications may result in severe illness, including fatal outcomes. During 2010–2018, an estimated 4.3–23 million medical visits, 140,000–960,000 hospitalizations, and 12,000–79,000 deaths were associated with influenza each year in the U.S. [8]. Another study estimated that 18,000–96,000 influenza-related intensive care unit (ICU) admissions occur annually in the U.S. [9]. There are an estimated 291,000–646,000 respiratory deaths attributed

* Correspondence: tmu0@cdc.gov
[2]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Mailstop H24-7, 1600 Clifton Road, N.E., Atlanta, GA 30329, USA
Full list of author information is available at the end of the article

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to seasonal influenza each year worldwide [2]. Here, we review strategies for prevention, diagnosis, and treatment of influenza virus infections in the ICU (Table 1).

## Risk factors

Influenza vaccination is the primary method for preventing influenza and reducing the risk of severe outcomes. In the U.S., the Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for all persons aged 6 months and older and prioritizes those at higher risk for influenza complications [10]. High-risk groups include adults aged ≥ 65 years [11, 12], children aged < 5 years (particularly those aged < 2 years) [13, 14], pregnant women (up to 2 weeks postpartum) [15–18], persons with certain chronic medical conditions, Native Americans/Alaska Natives,[1] and residents of nursing homes and other long-term care facilities (Table 2). Studies have specifically highlighted that those with chronic pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic or metabolic disorders, immunocompromised persons, children and adolescents receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome with influenza virus infection, and those who are extremely obese (BMI ≥ 40) are at increased risk for influenza-related complications [10, 19–23].

Many studies evaluated risk factors for severe influenza during the 2009 H1N1 influenza pandemic. Adult ICU patients with influenza A(H1N1)pdm09 virus infection were primarily non-elderly, were obese [24–28], and had higher odds of death, invasive mechanical ventilation, acute respiratory distress syndrome (ARDS), septic shock, and multi-lobar pneumonia when compared with seasonal influenza patients [24, 29]. In children, independent risk factors for influenza A(H1N1)pdm09-related mortality included chronic neurologic condition or immune compromise, acute myocarditis or encephalitis, and early presumed MRSA co-infection of the lung [30]. Female gender was also identified as a risk factor; however, there was no gender difference in overall mortality. Bacterial co-infection was identified in approximately one third of fatal influenza A(H1N1)pdm09 cases in the largest autopsy case series [31]. Bacterial co-infections in the inter-pandemic period are also common in critically ill influenza patients [32]. One study identified past or current tobacco use as a risk factor associated with ICU admission [33]. A recent multicenter cohort study reported that mortality was higher in immunosuppressed patients with influenza A(H1N1)pdm09 than in immunocompetent patients [34]. Severity of influenza seasons varies from year-to-year based on the predominant influenza viruses, and between seasonal and pandemic influenza [35, 36]. One study reported that patients with influenza A(H1N1)pdm09 had higher odds of severe disease than patients with either influenza A(H3N2) or influenza B virus infections [37]. However, influenza B virus infection has been shown to increase the odds of in-hospital mortality in children compared with influenza A virus infection [38].

**Table 1** Key points: care of patients with severe influenza

| Key Points |
|---|
| • There are an estimated 291,000–646,000 seasonal influenza-associated respiratory deaths every year worldwide. |
| • Annual influenza vaccination is the primary method of preventing influenza and influenza-related complications, especially in high-risk persons. |
| • Influenza molecular diagnostic testing is recommended for all patients requiring hospitalization with suspected influenza. |
| • Influenza antiviral treatment should be started as soon as possible in hospitalized patients with suspected influenza, including critically ill patients, and should not be delayed while awaiting results of influenza diagnostic tests. |
| • Enterically administered oseltamivir is recommended for influenza patients except for those with contraindications (e.g., gastric stasis, ileus, malabsorption). |
| • Repeat virologic testing in lower respiratory tract specimens may be required to determine therapeutic endpoints in ventilated patients with influenza |
| • Corticosteroids are not recommended for the routine treatment of influenza except when indicated for treatment of underlying medical conditions (e.g., COPD or asthma exacerbation) or septic shock. |

**Table 2** Groups at high risk for influenza complications*

| Risk factors for severe influenza outcomes |
|---|
| • Age < 5 years, especially those < 2 years |
| • Age ≥ 65 years |
| • Pregnant women |
| • Extreme obesity (BMI ≥ 40 kg/m$^2$) |
| • Native Americans/Alaskan Natives (may also apply to indigenous people from other countries) |
| • Current or past tobacco use |
| • Children and adolescents receiving aspirin or salicylate-containing medications who might be at risk for Reye syndrome |
| • Underlying chronic medical conditions: |
| ○ Pulmonary |
| ○ Cardiovascular |
| ○ Renal |
| ○ Hepatic |
| ○ Neurologic |
| ○ Hematologic |
| ○ Metabolic |
| ○ Immunocompromised state |

*From the U.S. Centers for Disease Control and Prevention Advisory Committee on Immunization Practices

## Prevention and vaccination

Influenza vaccination is recommended each fall for all persons aged ≥ 6 months in the U.S. and should continue

as long as influenza viruses are circulating in the community. Previously unvaccinated children aged 6 months through 8 years require two doses 1 month apart. Since influenza vaccine effectiveness (VE) to prevent medically attended illness varies from year-to-year by vaccine strain, age, prior immunity, and immune function, some vaccinated individuals can become symptomatic with influenza virus infection. However, several studies have reported influenza vaccine effectiveness in reducing illness severity, including reducing severe illness in persons aged ≥ 65 years [39], and reducing in-hospital mortality and ICU admissions for those aged 18–49 years and ≥ 65 years compared to unvaccinated individuals [40]. One study reported that duration of ICU hospitalization was reduced a half-day in patients aged 50–64 years who had received influenza vaccination compared with unvaccinated patients [41]. A study across all age groups in Spain reported influenza VE of 58% in reducing the risk of severe influenza requiring hospitalization [42]. A Southern Hemisphere study reported influenza VE of 82% in reducing influenza-associated ICU admissions among adults [43] while a study in Spain showed an adjusted influenza VE of 23% in preventing ICU admission and death [44].

Despite the benefits of influenza vaccination, there continues to be low vaccine coverage among adults admitted to the ICU who often have a high prevalence of high-risk comorbidities [45, 46]. In children, low influenza vaccination coverage has also been reported among those admitted to pediatric ICUs, even among those with underlying high-risk conditions [47]. Full influenza vaccination was shown to result in a 74% reduction in pediatric ICU admissions compared to unvaccinated or partially vaccinated influenza patients [47]. Furthermore, one study showed that influenza VE was 65% in reducing the risk of mortality in children aged 6 months to 17 years in the U.S. [48]. These data further emphasize the benefits of influenza vaccination in reducing severe influenza complications, especially in high-risk persons.

## Diagnosis

Persons with uncomplicated influenza typically experience acute onset of respiratory symptoms (cough, rhinorrhea, congestion), myalgias, and headache with or without fever. During influenza season, clinicians should also consider influenza when there is only fever present or in patients who are afebrile and have respiratory symptoms [49]. Complications of influenza vary by age, underlying comorbidities or high-risk conditions such as pregnancy, and immune function; elderly and immunocompromised persons may not always manifest fever. Critically ill patients may be admitted with respiratory or multi-organ failure, exacerbation of an underlying condition such as chronic lung disease [50, 51], heart failure [52], or other extrapulmonary complications including stroke, encephalopathy, or encephalitis [30, 49, 53].

Influenza testing is recommended for all patients requiring hospitalization with suspected influenza, including those admitted to the ICU during influenza season with acute respiratory illness and community-acquired pneumonia, without a clear alternative diagnosis. Furthermore, all individuals requiring critical care outside of influenza season should be tested for influenza if there is a possible epidemiological link to an individual with recent influenza, such as travel to areas with influenza activity or exposure to an institutional influenza outbreak. Special consideration should be given to elderly and immunocompromised patients, as influenza virus infection may not present with typical acute respiratory illness signs and symptoms (e.g., absence of fever). The Infectious Diseases Society of America (IDSA) 2018 Influenza Clinical Practice Guidelines also recommend influenza testing for patients at high risk of complications such as exacerbation of chronic cardiopulmonary disease [49]. Diagnosis of influenza should be made as soon as possible in critically ill patients, and initiation of antiviral treatment should not be delayed while awaiting results of diagnostic tests. Studies have reported an increase in mortality of ICU patients with influenza A(H1N1)pdm09 virus infection when diagnosis was delayed [54], and shorter hospital length of stay when antiviral treatment was initiated within 6 h of admission [55].

Several kinds of influenza diagnostic tests are available in clinical settings with variable sensitivities and specificities, including antigen detection assays, and molecular assays (nucleic acid detection) using respiratory tract specimens (Table 3). Within each of these testing categories, there is a wide range of available tests with varying diagnostic accuracy, and understanding the limitations of each diagnostic tool will allow the clinician to properly interpret their results. Most studies of influenza diagnostic accuracy have been conducted on specimens from patients with uncomplicated influenza, and few have assessed the performance of influenza tests in critically ill patients. The IDSA guidelines recommend molecular influenza assays for testing respiratory specimens from all hospitalized patients with suspected influenza because of their high sensitivity, specificity, and time to results (15 min to several hours) [49]. The use of rapid influenza molecular diagnostic testing can result in better outcomes for patients and reduce the amount of resources required to care for patients in the emergency room [57]. Serology and viral culture are not recommended for clinical decision making, because timely results will not be available to inform clinical management. Serology requires collection of appropriately paired acute and convalescent sera performed at specialized public health reference laboratories, and results based upon a single serum specimen are not interpretable [49]. Although viral culture can confirm the presence of infectious virus with very high sensitivity and

**Table 3** Influenza diagnostic tests

| Influenza testing modality[49, 56] | Method | Time to results | Sensitivity | Specificity | Respiratory specimens* | | |
|---|---|---|---|---|---|---|---|
| | | | | | Swab | Wash/fluid | Aspirate |
| Molecular assay (Rapid)**# | Nucleic acid amplification | 10–15 min | Moderate to high | High | NP or nasal | N/A | N/A |
| Molecular assay**# | Nucleic acid amplification | 15–30 min | High | High | NP or throat | NP or BAL/mini BAL | Nasal or endotracheal |
| Rapid influenza diagnostic Test (RIDT) | Antigen detection | 10–15 min | Low to moderate | High | NP, nasal, throat | NP or nasal | NP or nasal |
| Immunofluorescence assay (direct and indirect) | Antigen detection | 1–4 h | Moderate | High | NP | NP | Nasal |
| Rapid cell culture (shell vials; cell mixtures) | Virus isolation | 1–3 days | High | High | NP or throat | NP or BAL/mini BAL | Nasal or endotracheal |
| Tissue cell viral culture (conventional) | Virus isolation | 3–10 days | High | High | NP or throat | NP or BAL/mini BAL | Nasal or endotracheal |

*FDA-approved clinical specimens vary by specific test; refer to the manufacturer's package insert for each test's approved specimens
**Recommended for testing hospitalized patients with suspected influenza. Some molecular assays also detect other respiratory pathogens
#Patients with respiratory failure and suspected influenza should have lower respiratory tract specimens collected and tested, including if upper respiratory tract specimens are negative for influenza because a patient may have cleared influenza virus from the upper respiratory tract and continue to have influenza viral replication in the lower respiratory tract
*NP* nasopharyngeal, *BAL* bronchoalveolar lavage
Serologic testing is not recommended for diagnosis or clinical management of patients with suspected influenza

specificity, it must be performed at public health laboratories and requires 3–10 days to yield results.

A recent meta-analysis reported that influenza antigen detection tests that produce rapid results had very high specificities (> 98%), but sensitivities were highly variable compared with RT-PCR [58]. Rapid influenza diagnostic tests (RIDTs) without an analyzer device had only moderate sensitivity (53–54%), RIDTs that utilize an analyzer device (digital immunoassays) had moderately high sensitivity (77–80%), and rapid influenza molecular assays (nucleic acid detection) had high sensitivity (92–95%) [58]. Low sensitivity of RIDTs for detecting influenza virus in ICU patients has been reported [59]. Recently, a systematic analysis of rapid influenza molecular tests from 29 studies reported pooled sensitivity and specificity of 87.9% and 97.4%, respectively [60]. Therefore, antigen detection assays, such as rapid influenza diagnostic tests and immunofluorescence assays, are not recommended for hospitalized patients with suspected influenza because of their lower sensitivities, unless molecular assays are not available [49]. Negative results for influenza based on tests with low sensitivity (e.g., RIDTs, immunofluorescence assays) should not be used to make clinical decisions. Instead, negative test results should be followed up with reverse transcription polymerase chain reaction (RT-PCR) or other influenza molecular assays to confirm results, and antiviral treatment should continue until results are available.

Preferred respiratory specimens for influenza testing in hospitalized patients without lower respiratory tract disease include nasopharyngeal, mid-turbinate nasal, or combined nasal-throat swabs. Collection of lower respiratory tract specimens should be considered in hospitalized patients with suspected influenza if upper respiratory tract specimens are negative and a positive test would result in a change of clinical management [61], because viral replication in the lower respiratory tract may be ongoing and prolonged after virus is no longer detectable in the upper respiratory tract [24, 25]. Influenza A(H1N1)pdm09 virus in particular has been shown to have affinity for infecting the lower respiratory tract [24, 31]. In hospitalized patients receiving invasive mechanical ventilation in whom influenza is suspected, but not yet diagnosed, influenza testing should be performed on endotracheal aspirate specimens instead of those collected from the upper respiratory tract [61]. Molecular testing, including RT-PCR for influenza viruses can also be performed on bronchoalveolar lavage (BAL) fluid if collected for the testing of other pathogens. Blood, plasma, serum, cerebrospinal fluid, urine, and stool samples have very low diagnostic yield and are not recommended for influenza testing [49]. Diagnostic test results on specimens collected from non-respiratory sites should not be used for clinical decision making even for patients with extra-pulmonary complications of influenza.

Novel influenza A viruses are typically of animal origin, differ antigenically and genetically from currently circulating seasonal influenza A viruses (including H1N1pdm09 and H3N2 subtypes) and have infected at least one person. Novel influenza A viruses can cause a wide clinical spectrum of illness, ranging from asymptomatic infection, uncomplicated illness, to fulminant pneumonia, ARDS, and multi-organ failure [62] and human infection with a novel influenza A virus is of public health concern. In the U.S., human infection with a novel influenza A virus is nationally reportable to the Centers for Disease Control and Prevention; globally,

under the International Health Regulations, countries are required to report such human cases to the World Health Organization. A major concern is the risk of novel influenza A virus transmission among humans; depending upon the prevalence of pre-existing immunity in the population, novel influenza A viruses may have pandemic potential. Patients suspected with novel influenza A virus infection should be investigated for a possible epidemiological link, i.e., a history of recent exposure to poultry or pigs or close contact to an individual with suspected or confirmed novel influenza A virus infection. Novel influenza A virus infection cannot be distinguished from seasonal influenza A virus infection by clinical findings or testing at clinical laboratories and therefore requires specific molecular testing of respiratory specimens by RT-PCR at public health laboratories [63]. Cases of suspected novel influenza A virus infections should be discussed with appropriate local and or national public health and laboratory staff to coordinate the testing of appropriate respiratory specimens.

## Treatment of influenza

Treatment of severe influenza presents multiple challenges. The mainstay of therapy for patients with influenza is initiation of antiviral medication as soon as possible after illness onset [49]. Currently available FDA-approved antiviral medications include neuraminidase inhibitors (NAIs) (e.g., oral oseltamivir, inhaled zanamivir, and intravenous peramivir); cap-dependent endonuclease inhibitor (baloxavir marboxil); and adamantanes (e.g., amantadine and rimantadine) (Table 4). NAIs and baloxavir have activity against both influenza A and B viruses. Adamantanes only have activity against influenza A viruses and are not recommended for treatment of influenza due to widespread resistance among currently circulating strains of seasonal influenza A viruses. Notably, FDA-approved antiviral medications for treatment of influenza are approved for early treatment of uncomplicated influenza in outpatients based upon randomized placebo-controlled clinical trials conducted among previously healthy outpatients. Meta-analyses of randomized placebo-controlled clinical trials of early oseltamivir treatment of influenza in pediatric and adult outpatients have reported clinical benefit in reducing duration of illness and risk for some complications associated with influenza [65, 66].

No completed randomized, placebo-controlled trials of antiviral treatment have been conducted in hospitalized influenza patients to establish the efficacy of oseltamivir or other NAIs. A number of observational studies have

**Table 4** Antiviral treatment

| Antiviral agents and age group [64] | Treatment dosing |
|---|---|
| Oseltamivir | |
| Adults (including pregnancy) | 75 mg twice daily |
| Children (1 year or older) ≤15 kg | 30 mg twice daily |
| Children > 15–23 kg | 45 mg twice daily |
| Children > 23–40 kg | 60 mg twice daily |
| Children > 40 kg | 75 mg twice daily |
| Term Infants 0–11 months* | *See details in footnote* |
| Preterm infants** | *See details in footnote* |
| Zanamivir | |
| Adults | 10 mg (two 5-mg inhalations), twice daily |
| Children (≥ 7 years) | 10 mg (two 5-mg inhalations), twice daily |
| Peramivir | |
| Adults | 600 mg intravenous infusion once, given over 15–30 min |
| Children (2–12 years) | One 12 mg/kg dose, up to 600 mg maximum, intravenous, given over 15–30 min |
| Children (13–17 years) | 600 mg intravenous infusion once, given over 15–30 min |
| Baloxavir marboxil*** | |
| Adults and children (12 years or older) ≥40–80 kg | Single dose of 40 mg |
| Adults and children (12 years or older) ≥80 kg | Single dose of 80 mg |

*FDA-approved oral oseltamivir treatment dose for infants 14 days and older and less than 1 year old is 3 mg/kg per dose twice daily. The American Academy of Pediatrics has recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants 9–11 months of age

**Current weight-based dosing recommendations are not appropriate for premature infants. Please refer to American Academy of Pediatrics recommendations (https://pediatrics.aappublications.org/content/142/4/e20182367) for further information

***Safety and efficacy of baloxavir marboxil in patients less than 12 years old or weighing less than 40 kg have not been established. There are no data on balosavir treatment of hospitalized patients with influenza, and appropriate dosing frequency is unknown. A phase III clinical trial of baloxavir treatment of hospitalized influenza patients is ongoing: https://clinicaltrials.gov/ct2/show/NCT03684044

reported clinical benefit of neuraminidase inhibitors in hospitalized patients, including reduction in duration of hospitalization and risk of death, including in ICU patients [67–74]. Additionally, a systematic review of published reviews/meta-analyses reported survival benefit of NAI treatment in hospitalized patients [75], although another meta-analysis of observational studies did not [69]. In particular, a large pooled individual patient-level meta-analysis of observational studies from 38 countries identified a 38% reduction in risk of mortality in critically ill adults and those aged ≥ 16 years old when comparing early NAI treatment (< 48 h) with later treatment (> 48 h), and a 69% reduction in mortality risk between influenza patients receiving early NAI treatment and those who did not receive NAIs [72]. The mortality risk reduction of NAI treatment at any time versus no treatment was 28% for critically ill patients aged ≥ 16 years old; while a similar reduction in mortality was identified in critically ill children aged < 16 years, the result was not statistically significant [72] and was likely underpowered because death is less common in hospitalized children with influenza than in adults.

Although studies have shown the greatest clinical benefit when antivirals are started within 2 days of illness onset, some observational studies have shown clinical benefit of neuraminidase inhibitors when started up to 5 days following symptom onset [15, 55, 76, 77]. The large meta-analysis mentioned above also identified a significantly reduced mortality risk reduction (35%) in critically ill patients aged ≥ 16 years old who received NAI treatment > 48 h after symptom onset compared with those who did not [72]. A cohort study of early versus late oseltamivir treatment reported a significant reduction in mortality and median duration of ICU hospitalization in severely ill patients with influenza A(H3N2), but not A(H1N1pdm09) or B virus infection in Greece [78]. One French study reported delays in initiation of oseltamivir treatment prescribed to hospitalized influenza patients and suggested empiric administration of oseltamivir treatment in the emergency department for patients being admitted with lower respiratory tract disease during influenza season [79]. Overall, based upon available observational data to date in hospitalized patients with influenza, including ICU patients, initiation of neuraminidase inhibitor antiviral treatment is recommended as soon as possible for hospitalized patients with suspected or confirmed influenza.

Data on optimal dosing and duration of therapy with neuraminidase inhibitors are limited in critically ill influenza patients. Enterically administered oseltamivir is the preferred treatment for most hospitalized patients, given the lack of data for intravenous peramivir in this population. The use of inhaled zanamivir is not recommended in in critically ill patients due to the lack of data in hospitalized patients and the risk of bronchospasm in patients with underlying lung disease. Studies indicate that oseltamivir administered orally or via oro/naso-gastric tube is well absorbed in critically ill patients and reaches plasma levels comparable to those in ambulatory patients [80]. Similarly, several observational studies indicate that enteric oseltamivir reaches comparable plasma concentrations to non-critically ill patients in those receiving extracorporeal membrane oxygenation (ECMO) and renal replacement therapy [80–87], although dosing should be reduced in patients with significant renal impairment. There is scant evidence that increased NAI dosing (e.g., twice daily dosing) in critically ill patients provides additional clinical benefit than standard dosing [80, 88–92]. Of note, studies also suggest that increased oseltamivir dosing does not provide additional clinical benefit in obese adults, including extreme obesity (BMI > 40) [93, 94]. Duration of therapy can be difficult to define, as prolonged influenza viral replication and shedding from the both upper and lower respiratory tract can occur in critically ill patients [95, 96]. For this reason, it may be beneficial to continue antiviral therapy beyond 5 days, and repeat virologic testing may be beneficial in determining appropriate therapeutic endpoints [97]. Continuing antiviral treatment in critically ill patients until virus is not detectable in the lower respiratory tract may also help reduce the pro-inflammatory dysregulated cytokine response triggered by influenza virus infection and reduce nosocomial influenza virus transmission to healthcare personnel in the ICU. Consultation with a specialist with training in infectious diseases for the potential emergence of antiviral resistant virus infection should be considered for ICU patients with evidence of persistent influenza viral replication after NAI treatment, particularly in severely immunocompromised patients [49, 98].

For patients who cannot tolerate or absorb enteric oseltamivir due to gastric stasis, malabsorption, or other gastrointestinal processes, intravenous peramivir may be an alternative [99, 100]; however, studies have not identified an advantage for intravenous peramivir in comparison with enteric oseltamivir [101]. Notably, a randomized trial conducted in three influenza seasons found similar clinical outcomes between IV peramivir and enteric oseltamivir in hospitalized adult influenza patients [102]; a separate trial did not identify significant additional clinical benefit of peramivir in combination with standard-of-care therapy (which often included an NAI) [103]. A more recent, multicenter randomized controlled trial also found similar clinical benefit between enteric oseltamivir and intravenous peramivir in hospitalized influenza patients [104].

In 2018, a novel antiviral agent, baloxavir marboxil, was FDA-approved for early treatment of uncomplicated influenza in outpatients aged ≥ 12 years old. Baloxavir acts via inhibition of the influenza virus cap-dependent endonuclease, a different mechanism than the neuraminidase

inhibitors, and can treat NAI-resistant influenza virus infections. Randomized controlled trials of single-dose oral baloxavir showed similar clinical benefit to 5 days of twice-daily oral oseltamivir [105]. However, because these studies were limited to patients with uncomplicated influenza, the role of baloxavir monotherapy or in combination with an NAI for treatment of hospitalized influenza patients is unclear. Specifically, optimal dosing, duration of therapy, and appropriate endpoints have yet to be determined for baloxavir treatment of hospitalized influenza patients. In the outpatient RCT, patients treated with single-dose baloxavir showed significant reduction in influenza viral levels in the upper respiratory tract at 24 h compared with those receiving placebo or oral oseltamivir [105]. However, it is unknown whether this reduction in influenza viral shedding correlates with reduced transmissibility. A potential concern for the use of baloxavir in critically ill patients is the rapid development of resistance observed during the outpatient clinical trials [106]. A trial to assess the efficacy and safety of baloxavir in combination with oseltamivir versus oseltamivir monotherapy in hospitalized influenza patients is currently enrolling participants [107].

There are no completed randomized clinical trials of adjunctive corticosteroid treatment in influenza patients. A trial of corticosteroid therapy was planned during the 2009 H1N1 pandemic, but was halted due to limited number of enrolees [108]. One observational study in China during the 2009 H1N1 pandemic reported that administration of parenteral glucocorticoids within 72 h of illness onset tripled the risk of developing critical illness or death from influenza A(H1N1)pdm09 virus infection [109]. A re-analysis of prospectively collected data on 1846 influenza patients admitted with primary influenza pneumonia to 148 ICUs in Spain during 2009–2014 using propensity scoring matching reported that corticosteroid use was significantly associated with ICU mortality [110]. Meta-analyses of observational studies have concluded that that corticosteroid treatment of hospitalized influenza patients does not result in better outcomes and may be associated with adverse outcomes including increased mortality [111–113]. Similarly, a retrospective observational study conducted on critically ill children during the 2009 H1N1 pandemic found that high-dose (equivalent to 2 mg/kg per day of methylprednisolone) corticosteroid treatment was associated with mortality in the ICU, although a causative relationship was not determined [30]. A selection of individual observational studies in critically ill children and adults have also reported potential association between corticosteroid treatment and adverse influenza outcomes [30, 114, 115]. A recent Cochrane review of available observational studies suggested increased mortality when adjunctive corticosteroid therapy is used for influenza patients; however, the available evidence was of low quality and the authors suggest interpreting these results with caution [116].

Multiple studies have reported that corticosteroid treatment is associated with prolonged influenza viral shedding in hospitalized patients [117–119], including in sporadic human infections with avian influenza A(H7N9) virus in China [120], and increased rates of secondary bacterial and fungal co-infections [121, 122], which may lead to adverse clinical outcomes. However, there is some evidence to suggest that the increased risk attributed to corticosteroid treatment is a result of bias in observational studies. A large, retrospective study of critically ill adults in Canada found an increased risk of mortality in patients receiving corticosteroids; however, after adjusting for time-dependent differences between groups, no significant differences in mortality were observed with corticosteroid treatment [123]. Moreover, potential differences between low-dose and medium-/high-dose corticosteroid treatment are not well understood. One observational study of hospitalized patients with viral pneumonia due to avian influenza A(H7N9) virus infection in China reported that high-dose, but not low or moderate-dose corticosteroids, was associated with increased 30-day and 60-day mortality [124]. Currently, on the basis of available observational data to date, adjunctive corticosteroid treatment is not recommended for children or adults hospitalized with influenza, including critically ill patients, unless clinically indicated for another reason, such as treatment of asthma or COPD exacerbation or septic shock [49]. Further studies are required to understand the clinical benefit or harms associated with corticosteroid treatment of critically ill influenza patients.

Although neuraminidase inhibitors (oseltamivir) are currently recommended for antiviral treatment of influenza in hospitalized patients based on observational studies, including in critically ill patients, there are a number of novel strategies and products for treating influenza in various stages of development. One approach under investigation is triple-combination antiviral drug (TCAD) therapy, which combines amantadine, ribavirin, and oseltamivir for treatment of influenza in critically ill and high-risk patients. Unfortunately, studies to date have not shown a benefit of TCAD over oseltamivir monotherapy [125–127]. Several novel antiviral compounds are in various stages of investigation, including small-molecule polymerase inhibitors such as pimodivir [128] and favipiravir [129]. A number of monoclonal and polyclonal antibodies, targeted against a variety of influenza viral proteins, are also in development [130–133]. Similarly, convalescent plasma has shown potential benefit in the treatment of severe influenza, and further trials are underway [134–136]. Another area of intense interest is the modification of the host antiviral response to

influenza virus infection. There are ongoing preclinical and clinical studies of a variety of other immunomodulatory agents for treatment of influenza, including celecoxib [137], statins, etanercept, pioglitazone, azithromycin [138], and interferons [139].

## Conclusions

Influenza vaccination can reduce the risk of complications from influenza, including reducing illness severity and the risks of hospitalization, ICU admission, and death. The elderly, young children, pregnant women, and those with underlying medical conditions are most at risk for severe complications of influenza. A diagnosis of influenza should be considered in critically ill patients admitted with complications such as exacerbation of underlying chronic comorbidities, community-acquired pneumonia, and respiratory failure during influenza season. Influenza molecular assays are recommended for testing upper respiratory tract specimens in patients without signs of lower respiratory tract disease. However, because critically ill patients with lower respiratory tract disease may have cleared influenza virus in the upper respiratory tract, but have prolonged influenza viral replication in the lower respiratory tract, an endotracheal aspirate (preferentially) or bronchoalveolar lavage fluid specimen (if collected for other diagnostic purposes) should be tested by molecular assay. Antiviral treatment with standard-dose oseltamivir delivered orally or enterally by oro or naso-gastric tube is recommended as soon as possible for patients with suspected influenza without waiting for testing results. Corticosteroids should not be routinely administered for treatment of influenza and should only be given for other indications (e.g., exacerbation of asthma or chronic obstructive pulmonary disease, or septic shock), because of the risk for prolongation of influenza viral shedding and ventilator-associated pneumonia in critically ill influenza patients with respiratory failure. Future directions for treatment of influenza in critically ill patients include novel antiviral compounds, combination antiviral treatment with drugs with different mechanisms of action, immunomodulatory agents, and strategies for multimodality, combination antiviral, and host-directed immunomodulatory therapies.

## Endnotes

[1]These risk factors are included in the U.S. CDC's Advisory Committee on Immunization Practices recommendations for influenza vaccination. This may also apply to indigenous people from other countries, including indigenous Australians and First Nations people.

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**Author details**
[1]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, GA, USA. [2]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Mailstop H24-7, 1600 Clifton Road, N.E., Atlanta, GA 30329, USA.

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