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Influenza

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Annual seasonal influenza epidemics of variable severity caused by influenza A and B virus infections result in substantial disease burden worldwide. Seasonal influenza virus circulation declined markedly in 2020–21 after SARS-CoV-2 emerged but increased in 2021–22. Most people with influenza have abrupt onset of respiratory symptoms and myalgia with or without fever and recover within 1 week, but some can experience severe or fatal complications. Prevention is primarily by annual influenza vaccination, with efforts underway to develop new vaccines with improved effectiveness. Sporadic zoonotic infections with novel influenza A viruses of avian or swine origin continue to pose pandemic threats. In this Seminar, we discuss updates of key influenza issues for clinicians, in particular epidemiology, virology, and pathogenesis, diagnostic testing including multiplex assays that detect influenza viruses and SARS-CoV-2, complications, antiviral treatment, influenza vaccines, infection prevention, and non-pharmaceutical interventions, and highlight gaps in clinical management and priorities for clinical research.

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Introduction

Influenza is an acute viral respiratory disease caused by infection of the respiratory tract with influenza viruses (seasonal influenza A and B viruses) that circulate among people worldwide. Seasonal influenza refers to disease in humans caused by infection with seasonal influenza A or B viruses and is the focus of this Seminar. Annual influenza epidemics of variable severity typically occur during colder periods in temperate climates worldwide.[1] Year-round influenza activity can be observed in tropical and subtropical areas, peaking at different times.[1] Most people with influenza have self-limited upper-respiratory-tract symptoms with or without systemic signs and symptoms that temporarily affect daily activities, including missing work or school, and some might access medical care. Some individuals with influenza, particularly young children, older adults, pregnant people, and those with certain underlying conditions, can have complications resulting in medical care visits, hospital admissions, or in-hospital and community deaths.[2]

Virology

Of the four types of influenza viruses (A–D) within the *Orthomyxoviridae* family, three types (A, B, and C) infect and cause disease in humans. Type A and B viruses that cause epidemics worldwide are referred to as seasonal influenza viruses. Influenza viruses are enveloped viruses encoded by segmented negative-sense RNA genomes. The eight viral RNA segments of influenza A and B viruses are translated into 12 proteins. Influenza A viruses infect many avian and some mammalian species and can cause rare pandemics in humans; influenza B viruses primarily infect humans.[2] Influenza C viruses infect humans and pigs and dogs.[3] Influenza D viruses primarily infect cattle with spillover to other animals. Whether influenza D viruses can infect and cause disease in people is unclear, but detection of antibodies to influenza D virus has been reported in people exposed to cattle.[4] Influenza A viruses are divided into subtypes on the basis of the haemagglutinin and neuraminidase surface glycoproteins. Currently, influenza A(H1N1)pdm09 and A(H3N2) viruses circulate among people worldwide. The haemagglutinin protein is the major antigen that contains the sialic-acid-receptor binding site, and the neuraminidase aids in release of viral particles from infected cells. Influenza B viruses circulating among humans are divided into two lineages, B/Victoria/2/87 and B/Yamagata/16/88, but B/Yamagata viruses have not been detected since March, 2020.

Of the 18 haemagglutinin and 11 neuraminidase subtypes identified to date, 16 haemagglutinin (H1–16) and nine neuraminidase (N1–9) subtypes are enzootic in avian species, primarily wild waterfowl, and these viruses periodically infect animals such as poultry and pigs and establish enzootic and endemic lineages. The high error rate of the RNA-dependent RNA polymerase (RDRP) and reassortment of RNA segments during co-infections provide influenza A viruses with evolutionary power and can facilitate circulation among a new host. Both intrasubtype and intersubtype genetic reassortment occur and can rapidly select for influenza A viruses with

Search strategy and selection criteria

We searched PubMed for articles on influenza published in English from May 1, 2016, to April 31, 2022, on the topics included in the Seminar using the search terms "influenza", "influenza and systematic reviews", "influenza and diagnosis", "influenza and therapy", "influenza and prevention and control", "influenza and pandemic", "influenza and epidemiology", "influenza and complications", "influenza and clinical", "influenza clinical management", "influenza and vaccines", "influenza vaccine effectiveness", "influenza and pandemic", "influenza and transmission", and "influenza and risk factors", "influenza surveillance", "influenza disease burden", "influenza hospitalizations", "influenza mortality", "influenza and diagnostic testing", "influenza virology", "influenza pathogenesis", "influenza complications", "influenza treatment", "influenza and antiviral treatment", "influenza and COVID-19", "zoonotic influenza", "novel influenza A", and "influenza pandemic preparedness". The most relevant and recently published references were prioritised for inclusion. Relevant key articles older than 5 years were included when indicated.

improved fitness. H17N10 and H18N11 virus subtypes were identified in new-world bats;[5] however, these viruses use different receptors and have other features not common to influenza A viruses.[6]

Seasonal influenza A and B viruses primarily evolve to escape human humoral immunity via amino-acid substitutions, insertions, or deletions coding for haemagglutinin and neuraminidase epitopes that enable the viruses to escape key antibodies induced through previous infections, vaccinations, or both. This evolutionary process is known as antigenic drift and drives annual influenza epidemics. Antigenic shift refers to human infection with a novel influenza A virus containing a haemagglutinin that is antigenically and genetically different from circulating seasonal influenza A viruses. Interspecies transmission in animals can result in genetic reassortment of viral RNA segments during co-infections with different influenza A viruses and this is central to the emergence of novel influenza A viruses, typically through zoonotic transmission. Host species-specific determinants affect the pandemic potential of influenza A viruses circulating among animals.[7] Crucial determinants are the ability for a viral haemagglutinin to efficiently bind α2,6-linked sialic acids (highly expressed by epithelial cells in the upper respiratory tract of humans),[8–10] and for the RDRP to transcribe and replicate the RNA genome efficiently.[10] If the novel influenza A virus has the ability for sustained human-to-human transmission and most of the population does not have immunity to the novel virus, a pandemic can occur. Global surveillance for influenza viruses is crucial to monitoring antigenic drift and emergence of novel influenza A viruses (appendix pp 1–2).

See Online for appendix

Transmission dynamics and modalities

The basic reproduction number for seasonal influenza is estimated to be approximately 1·3,[11] with mean serial intervals for symptomatic influenza A virus infections of 2·2 and 2·8 days.[12] A systematic review estimated the median incubation period to be 1·4 days for influenza A and 0·6 days for influenza B.[13] Slightly longer incubation periods have generally been considered; for example, in human challenge studies, symptoms scores peak 2–3 days after influenza A virus inoculation.[14] Seasonal influenza A and B viruses are generally believed to be transmitted at a short range (1–2 metres) from person to person through large (≥5 μm) droplets and small-particle (<5 μm) droplet nuclei (aerosols) that are expelled by infected people through coughing.[15] Detection of infectious virus from exhaled breath of symptomatic individuals suggests potential for aerosol transmission.[16] Influenza viruses in aerosols and droplets can remain infectious for several hours at low and high relative humidity under experimental conditions.[17,18] The role of contact transmission and fomite spread is not well understood but is theoretically possible because animal studies have detected viral aerosolisation from fomites,[19] demonstrated efficient aerosol transmission,[20] and influenza viral RNA has been detected on surfaces,[21] including recovery of infectious virus from mobile phones of people with influenza.[22]

Influenza virus concentrations in the upper respiratory tract are highest at illness onset or 1–2 days after illness onset and then decline substantially within 3 days for influenza A but can remain higher for influenza B in immunocompetent individuals.[23,24] Young infants can shed influenza virus for more than 1 week and severely immunocompromised people can have prolonged viral shedding for weeks to months.[25,26] Duration of influenza-virus detection increases with severity of illness.[27] Influenza viruses can be detected in the upper respiratory tract of some people who are infected before symptom onset,[24] but the contribution of transmission from presymptomatic and asymptomatic people who are infected is unclear. Influenza viral RNA concentrations in the upper respiratory tract are lower, and duration of viral RNA detection is shorter, for individuals who are asymptomatic or paucisymptomatic, versus those with more influenza symptoms.[28] A systematic review of influenza-virus transmission in households reported a wide range (1–38%) of secondary infection risk.[29] A study of households in South Africa reported that secondary transmission was highest from symptomatic index cases with two or more symptoms and from children aged 1–4 years; among households with asymptomatic index cases, influenza virus infection was identified in 6% of household contacts, accounting for 27% of all secondary household infections.[30]

Epidemiology and disease burden

Influenza epidemics occur annually during relatively cooler and lower humidity periods in temperate climates of the northern and southern hemispheres, whereas in tropical and subtropical climates, one or more peaks in influenza activity during higher absolute humidity or higher precipitation months and year-round influenza activity can occur.[1,31] Influenza outbreaks can occur during interepidemic periods among people who are epidemiologically linked to travel to areas with influenza activity, including people in congregate settings. In the USA, annual incidence of symptomatic influenza is estimated to vary from 3% to 11%.[32] Household-based and community-based studies in different countries have shown that influenza virus infections and illness rates are highest in children and decrease with increasing age, approximately 20–40% of symptomatic people can manifest influenza-like illness (fever and cough or sore throat), whereas up to half of people with symptomatic illnesses can experience acute upper-respiratory-tract symptoms without fever, and the asymptomatic proportion can range from 14% to more than 50%.[24,28,30,33]

The severity of influenza epidemics varies widely. Because of limitations in influenza testing and the small percentage of people with influenza who are tested, modelling studies based on surveillance data are used to

estimate disease burden. In the USA, in 2010–20, estimated influenza-related symptomatic illnesses, medical visits, hospitalisations, and deaths ranged from 9·3 to 41·0 million, 4·3 to 21·0 million, 140 000 to 710 000, and 12 000 to 52 000, respectively, per year.[34] A systematic review and meta-analysis estimated that more than 32 million cases and 5·7 million hospitalisations occur from influenza-associated lower-respiratory-tract disease in adults worldwide each year, with the highest hospitalisation rates in people aged 65 years or older.[35] A systematic review estimated that among nearly 110 million influenza illnesses, 870 000 hospitalisations, more than 15 000 in-hospital deaths, and approximately 35 000 deaths caused by acute lower-respiratory-tract disease worldwide occurred in children younger than 5 years in 2018, with most influenza in-hospital deaths occurring in low-income and middle-income countries.[36] Epidemics caused by influenza A(H3N2) viruses are associated with higher morbidity and mortality in older adults and epidemics caused by antigenically drifted A(H3N2) viruses can also cause higher morbidity and mortality in children.[37]

In the USA, hospitalisation rates for laboratory-confirmed influenza are typically highest among people aged 65 years and older, children younger than 5 years, and people aged 50–64 years, with the highest mortality rate in people aged 65 years and older. Among US children, incidence of hospitalisation and in-hospital mortality rates are highest in infants younger than 6 months.[38] It has been estimated that approximately 300 000 influenza-associated respiratory deaths occur worldwide each year, with the highest estimated regional influenza-associated mortality rates in sub-Saharan Africa and southeast Asia.[39] However, the numbers of influenza-related respiratory hospital admissions and deaths underestimate non-respiratory complications, such as exacerbation of underlying chronic conditions or major adverse cardiovascular events associated with influenza,[40] particularly in older adults, and limited influenza testing can underestimate both mild and severe influenza-associated illnesses. For example, in a small Spanish study that tested respiratory specimens from deceased older adults in morgues, 10 of 57 were positive for influenza A(H3N2) virus infection, of whom only one had been diagnosed with influenza before death.[41]

In the USA, children younger than 5 years, people aged 65 years or older, pregnant people up to 2 weeks post partum, immunocompromised people, people with certain chronic comorbidities (eg, pulmonary, cardiac, neurological, metabolic, haematological, and extreme obesity), and long-term care-facility residents are considered to be at increased risk for influenza complications that might require hospital admission or lead to death (appendix p 8).[42] Among women of reproductive age hospitalised with influenza over nine seasons in the USA, nearly 28% were pregnant, and 62% were in their third trimester.[43] Pregnant people can have premature labour and fetal loss, and severe pneumonia with influenza, particularly in the third trimester up to about 2 weeks post partum,[44,45] although a meta-analysis reported that pregnant people were at higher risk of hospitalisation, but not intensive-care-unit (ICU) admission or death compared with non-pregnant people.[46] Non-Hispanic Black people younger than 75 years are more likely to be hospitalised and admitted to an ICU for influenza-related complications than White people in the USA.[47] Similarly, people who are American Indian or Alaska Native younger than 50 years are more likely to be hospitalised or admitted to an ICU than White people, and hospitalisation rates for those younger than 5 years are higher for Black, Hispanic, American Indian or Alaska Native, and Asian or Pacific Islander children than for White children in the USA.[47] The average economic cost associated with annual influenza epidemics in the USA was estimated to be US$11·2 billion, with indirect costs (eg, absenteeism from paid employment) substantially higher than direct medical-care costs.[48]

Diagnostic testing

Clinical diagnosis of influenza is often inaccurate because of overlapping symptoms from infections with other cocirculating respiratory pathogens, including SARS-CoV-2. Influenza testing can aid clinical decisions, but results, especially negative results, should be properly interpreted in the context of predictive values that consider the prevalence of influenza viruses in the tested population, test sensitivity, and specificity.[26] Upper-respiratory-tract specimens from outpatients should ideally be collected within 4 days of illness onset, but viral RNA might be detectable for longer periods, particularly in young children and immunocompromised people. Nasopharyngeal specimens have the highest yield for influenza viruses, but a mid-turbinate nasal swab or combined nasal and throat swabs are acceptable specimens, depending upon the test. In patients hospitalised with respiratory failure, lower-respiratory-tract specimens should be tested if upper-respiratory-specimens are negative.[26]

Several diagnostic tests detect influenza viruses in respiratory specimens (table 1). Point-of-care (PoC) rapid antigen-detection tests detect influenza viral proteins in upper-respiratory specimens, are simple, and can produce quick results, but have lower sensitivity and lower negative predictive values than RT-PCR.[26,49] Nucleic-acid amplification assays (molecular assays), including RT-PCR and loop isothermal amplification, have high sensitivity and high specificity, can detect influenza viruses for longer periods than antigen tests and can produce prompt results within 15–20 min (for PoC use) or up to several hours.[26,50] Multiplex antigen tests and molecular assays can detect and distinguish influenza A, influenza B, and SARS-CoV-2 infections (and identify co-infections), and can be very useful when SARS-CoV-2 and influenza viruses are cocirculating for testing of outpatients and patients who

	Method	Accuracy*	Comments
Rapid antigen test (10–15 min to results)	Influenza viral antigen detection by antibodies using a lateral flow immunoassay or rapid immunofluorescent assay, often with a digital analyser device	Low-to-moderate sensitivity (40–80%) and high specificity	Can detect and distinguish influenza A and B virus infection; sensitivity is higher for tests that use an analyser device; available for point-of-care use; and multiplex tests can detect and distinguish among SARS-CoV-2 and influenza A and B virus infections
Rapid molecular assay (15–40 min to results)	Influenza viral RNA detection using nucleic acid amplification; requires a small-footprint machine with an embedded analyser device	High sensitivity (>95%) and high specificity (>99%)	Can detect and distinguish influenza A and B virus infection; some assays are available for point-of-care use; multiplex tests can detect and distinguish among SARS-CoV-2 and influenza A and B virus infections; and some assays can also detect RSV
Molecular assay (45–80 min to results; up to 4–6 h for some assays) done in clinical laboratories	Influenza viral RNA detection using nucleic acid amplification; some assays require complex machinery, preanalytical nucleic-acid extraction, and downstream analysis	High sensitivity (>95%) and high specificity (>99%)	Can detect and distinguish influenza A and B virus infection; must be done in a certified clinical laboratory or public health laboratory; requires qualified laboratory personnel; multiplex assays can detect and distinguish among SARS-CoV-2 and influenza A and B virus infections; and some multiplex assays can also identify influenza A virus subtypes and other respiratory virus and bacterial pathogens
Immunofluorescence assay (1–4 h to results)	Influenza viral antigen detection by antibodies using immunofluorescent staining; requires collection of upper-respiratory-tract cells and fluorescent microscope	Moderate sensitivity and high specificity	Can detect and distinguish influenza A and B virus infection; must be done in a certified clinical laboratory or public health laboratory; requires qualified laboratory personnel; requires skilled staff; sensitivity depends upon sample preparation; and less commonly used
Virus culture (1–10 days to results); requires qualified personnel, usually done at public health laboratories	Isolation of viable influenza virus using tissue cell culture	High sensitivity and high specificity	Can detect and distinguish influenza A and B virus infection; requires complex laboratory space suitable for virus propagation; shell-vial cell culture can yield results in 1–3 days; and standard tissue cell culture might require 3–10 days

For respiratory specimens. Adapted from the Centers for Disease Control and Prevention.[49] RSV=respiratory syncytial virus. *Compared with RT-PCR. Negative results do not necessarily rule out influenza virus infection; results should be interpreted in the context of influenza prevalence in the population being tested and the signs and symptoms of the patient, underlying medical conditions, specimen source, and test characteristics (sensitivity and specificity).

Table 1: **Influenza diagnostic tests**

were hospitalised presenting with acute respiratory illness (appendix pp 9–10). Tissue-cell viral culture of respiratory specimens does not yield timely results for clinical decision making, but is essential for antigenic characterisation and candidate vaccine development. Serology can establish a retrospective diagnosis of influenza, but requires collection of acute and convalescent sera, must be done at specialised laboratories, cannot produce timely results to inform clinical management, and is not recommended except for vaccine studies and epidemiological investigations.[26]

Use of PoC influenza tests outside of health-care facilities such as at pharmacies can facilitate prompt initiation of antiviral treatment.[51] Home self-collection of nasal swabs can yield similar influenza testing results to swab collection by trained research staff.[52] Influenza rapid-antigen tests and molecular assays that use smartphone technology are under development for home use with self-collected nasal swabs; ideally, results are transmitted in real time to a physician to facilitate rapid prescription of antiviral treatment and are included in the patient's electronic health record.[53] Other diagnostic innovations are in development (appendix p 5).

Clinical spectrum and clinical complications

The clinical spectrum of seasonal influenza ranges from asymptomatic infection, uncomplicated upper-respiratory-tract symptoms with or without fever, to complications that can result in severe disease (table 2). Fever might not be present in many people who are symptomatic, particularly in older adults and people who are immunocompromised. Systemic signs and symptoms, such as fever, chills, myalgia, malaise, and headache typically occur abruptly with respiratory symptoms such as dry cough, sore throat, and nasal discharge.[2] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, and abdominal pain can occur in children. Ocular symptoms such as lacrimation, conjunctivitis, photophobia, and painful eye movement are less common.[54] Rashes have been described but are uncommon. Older adults might present with general symptoms such as malaise, anorexia, dizziness, and weakness without fever, sore throat, and myalgia. Signs and symptoms of uncomplicated influenza typically resolve after 3–7 days for most people,[2] although cough and malaise can persist for more than 2 weeks, especially in older adults and those with chronic lung disease.

Respiratory complications

Influenza is associated with a wide range of respiratory complications. In children, croup, bronchiolitis, tracheitis, and otitis media can occur. In all ages, both primary influenza viral pneumonia (appendix p 6) and influenza viral co-infection with community-acquired bacterial pneumonia (appendix p 7; most commonly with *Streptococcus pneumoniae* or *Staphylococcus aureus*, methicillin-sensitive or methicillin-resistant staphylococcus aureus [MRSA], including Panton Valentine leucocidin-producing MRSA) can lead to respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure.[26,55,56] Community-acquired secondary bacterial pneumonia is more common with influenza than with COVID-19 in

patients requiring hospitalisation.[57,58] Influenza-virus infection can exacerbate asthma, chronic obstructive pulmonary disease, and cystic fibrosis.

Co-infection with other respiratory viruses can occur, particularly in children, and influenza virus and SARS-CoV-2 co-infection can result in more severe disease in adults than either SARS-CoV-2 or influenza virus infection alone.[59,60] Invasive fungal co-infection can also result in critical illness and high mortality, particularly in patients treated with corticosteroids and people who are immunocompromised, and has been reported with widely variable frequency in different countries.[61] Hospital-acquired infection with multidrug-resistant bacteria causing ventilator-associated pneumonia is a severe complication in patients who are critically ill with influenza.

Non-respiratory complications

Patients of all ages with influenza can experience dehydration and exacerbation of underlying chronic disease (eg, heart failure, coronary artery disease, cerebrovascular disease, and diabetes). Cardiac complications of influenza that can result in critical illness and fatal outcomes include acute ischaemic heart disease, myocardial infarction, and heart failure in people with pre-existing cardiovascular disease, and myocarditis and pericarditis without underlying cardiac disease.[40,62] Musculoskeletal complications include mild-to-severe myositis, and uncommonly, rhabdomyolysis. Elevation of hepatic aminotransferases, can occur with severe disease, but hepatic failure is rare. A wide range of neurological complications have been described shortly after influenza symptom onset or with onset in the second week or later; encephalopathy, encephalitis, transverse myelitis, and acute disseminated encephalomyelitis are more common in children than in adults.[63,64] Influenza can precipitate febrile seizures in young children and status epilepticus in people with seizure disorders. Transient altered mental status, encephalopathy with full recovery, and fulminant acute necrotising encephalitis with neurological sequelae or brain death can occur.[65] Uncommon neurological complications include Guillain-Barré syndrome,[66] and Reye syndrome (with salicylate exposure in children more commonly associated with influenza B than influenza A). Severe illness from toxic shock syndrome associated with *S aureus* or group A *Streptococcus* has been reported with influenza, and an association of influenza and meningococcal disease has been reported.[67] Acute kidney injury requiring renal replacement therapy can complicate respiratory failure. Sepsis and septic shock can occur with influenza, with or without invasive bacterial co-infection.

	Complications	Considerations
Upper-respiratory complications	Otitis media, parotitis, sinusitis, and laryngotracheobronchitis	Otitis media, parotitis, and laryngotracheobronchitis are more common in children than adults
Lower-respiratory complications	Bronchiolitis, bronchitis, reactive airway disease, pneumonia, respiratory failure, and acute respiratory distress syndrome	Bronchiolitis is more common in young children than in adults
Cardiac complications	Myocardial infarction, myocarditis, pericarditis, and heart failure	Influenza might precipitate myocardial infarction or heart failure in people with coronary artery disease; cardiac complications can result in critical illness with fatal outcomes
Gastrointestinal complications	Hepatitis, pancreatitis, and severe acute abdomen-like pain	Hepatic failure is rare
Musculoskeletal complications	Myositis, rhabdomyolysis, and compartment syndrome	Severe myositis (soleus and gastrocnemius) can occur in school-age children; myoglobinuria can cause acute kidney injury
Renal complications	Acute kidney injury and kidney failure	Can occur with severe pneumonia
Neurological complications	Encephalopathy, encephalitis, meningoencephalitis, febrile seizures, cerebrovascular accident, transverse myelitis, acute demyelinating encephalomyelitis, Reye syndrome with salicylate exposure, and Guillain-Barré syndrome	Encephalopathy and encephalitis are more common in young children, can be acute or postinfectious with full neurological recovery, sequelae, or fatal outcomes; Reye syndrome is rare in children without salicylate exposure, and Guillain Barre syndrome is uncommon
Co-infections	Pneumonia, ventilator-associated pneumonia, tracheitis, and meningitis	Invasive bacterial, viral, and fungal coinfections can cause critical illness and fatal outcomes
Other complications	Exacerbation of chronic disease, dehydration, sepsis, toxic shock syndrome, sepsis-like syndrome or sudden death in young infants, premature labour, and fetal loss in pregnant people	People of all ages with chronic disease can experience worsening of underlying conditions (eg, chronic obstructive pulmonary disease exacerbation in adults, acute chest syndrome with sickle cell disease, worsening of asthma, and heart failure)

Adapted from Uyeki and colleagues.[26]

Table 2: **Complications associated with influenza**

Pathogenesis

Host factors (eg, age, genetics, overall health, immune history with influenza virus, and immunological function) influence severity of influenza virus infections. Severe disease can occur among infants and young children who do not have immunity from infection or vaccination, whereas immunosenescence occurs in older adults and people who are immunocompromised. Influenza virus infection might exacerbate chronic conditions such as coronary artery disease and chronic obstructive pulmonary disease. Pregnancy (ie, third trimester), cardiovascular disease, diabetes, and obesity can impair T-cell responses that induce chronic inflammation with persistently elevated concentrations of proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor α.

Immunity resulting from first exposure to influenza viruses (termed original antigenic sin)[68] has an important effect on pathogenesis because the first influenza A virus infection experienced in childhood can generate lifelong immunological memory to many different epitopes on several viral proteins, providing protection from antigenically similar influenza A viruses, although not necessarily against infection by antigenically drifted or novel influenza A viruses, but protection might be conferred against severe disease.[69] During the 1918 H1N1 pandemic, young adults without previous exposure to

	Dosing	Mechanism of action	Considerations
Oseltamivir (oral suspension or capsule)	Duration of treatment, 5 days; age <1 year, 3 mg/kg twice per day; age ≥1 year and weight ≤15 kg, 30 mg twice per day; weight 16 kg to 23 kg, 45 mg twice per day; weight 24 kg to 40 kg, 60 mg twice per day; weight >40 kg, 75 mg twice per day; and adults, 75 mg twice per day	Inhibits influenza viral neuraminidase; blocks release of progeny virions from infected respiratory epithelial cells	Widely available in generic formulation; can be administered enterically via orogastric or nasogastric tubes; recommended for pregnant people; recommended for patients who are hospitalised; no completed fully enrolled placebo-controlled trials; increased risk of nausea or vomiting; dosage should be adjusted for patients with reduced creatinine clearance or receiving dialysis; can be given for prophylaxis after exposure once per day for 7 days; and might have lower effectiveness against influenza B virus infections
Zanamivir* (inhaled powder)	Duration of treatment, 5 days; age ≥7 years, 10 mg (two inhalations) twice per day	Inhibits influenza viral neuraminidase; blocks release of progeny virions from infected respiratory epithelial cells	Less available than oseltamivir; contraindicated in people with chronic airway disease because of increased risk of bronchospasm; insufficient data for patients who are hospitalised; intravenous zanamivir might be available in some countries; and laninamivir (single inhalation) is a related long-acting inhaled neuraminidase inhibitor approved for treatment of influenza in Japan
Peramivir (intravenous)	Duration of treatment, single dose via intravenous infusion; age 6 months to 12 years, 12 mg/kg up to 600 mg; and age ≥13 years, 600 mg	Inhibits influenza viral neuraminidase; blocks release of progeny virions from infected respiratory epithelial cells	Less available than oseltamivir; insufficient data for patients who are hospitalised
Baloxavir (oral suspension or capsule)	Duration of treatment, single dose; age ≥5 years and weight <20 kg, 2mg/kg; weight 20 kg to <80 kg, 40 mg; and weight ≥80 kg, 80 mg	Inhibits cap-dependent endonuclease within the polymerase acidic-protein subunit of viral polymerase; blocks viral replication in infected cells	Similar clinical benefit to 5 days of oseltamivir; significantly reduces influenza viral RNA concentrations in the upper respiratory tract after single dose; greater efficacy against influenza B virus infection than oseltamivir; reduces some complications in patients at high risk; not recommended for pregnant people; not recommended as monotherapy in people who are severely immunocompromised; single dose can be given as prophylaxis after exposure

Check national recommendations for the availability of antivirals and differences in age approvals and duration of treatment, including in patients who are immunocompromised. Greatest clinical benefit is when treatment is started within 2 days of illness onset in outpatients with uncomplicated influenza. The information here is partially obtained from the Centers for Disease Control and Prevention.[80] *Intravenous zanamivir might be available in some countries. For example, intravenous zanamivir received marketing authorisation in the EU in 2019 for the treatment of patients aged 6 months or older with complications and potentially life-threatening influenza caused by influenza virus with known or suspected resistance to antivirals other than zanamivir, and, or when other antivirals, including inhaled zanamivir, are not suitable. Consult national recommendations for availability and indicated use.

Table 3: **Antiviral medications for treatment of influenza**

A(H1N1) viruses had high mortality rates. During the 2009 H1N1 pandemic, relatively lower disease severity was observed in older adults previously exposed in childhood to an A(H1N1) virus with antigenic similarity to the pandemic virus, and many B cells induced by infection or vaccination were derived from B-cell memory.[70] Certain genetic alleles of genes encoding proteins can increase disease severity risk, such as interferon-induced transmembrane protein 3,[71] transmembrane protease serine 2,[72] or pulmonary-surfactant-associated proteins.[73,74]

In most symptomatic influenza virus infections, the innate immune response triggered is balanced, cellular immunity is activated, and recovery is associated with adaptive immune responses. However, in some individuals, the immune response to influenza virus infection can be dysregulated, with activation of proinflammatory cytokines (especially IL-6) and chemokines that can cause pulmonary inflammation and acute lung injury, acute respiratory distress syndrome, sepsis, and multiorgan failure.[75] Influenza virus infection can activate host type 1 interferon-related pathways early in the clinical course of severe influenza, but this response can be diminished by activation of inflammatory neutrophilic and cell stress or apoptotic responses in patients who are critically ill.[76] Proinflammatory cytokines (eg, IL-6, IL-8, monocyte chemoattractant protein 1, and monokine-induced γ interferon) are higher in the lower respiratory tracts of patients with severe influenza compared to those with moderate disease.[77] Coagulation pathway abnormalities can be provoked by activation of endothelial cells and result in critical illness from vascular leak and disseminated intravascular coagulation, further contributing to inflammatory injury.[78] Bacterial co-infections and the microbiome further contribute to the pathogenesis and severity caused by influenza viruses.[55,76,79]

Treatment

The clinical benefit of antiviral treatment of influenza is greatest when started soon after illness onset. Antiviral drugs with activity against influenza A and B viruses include neuraminidase inhibitors, and a polymerase inhibitor (table 3). The neuraminidase inhibitors oseltamivir, zanamivir, laninamivir, and peramivir, differ by approved ages and availability in different countries, duration of treatment, routes of administration, and contraindications. By inhibiting the function of viral neuraminidase, neuraminidase inhibitors block release of progeny virions from infected respiratory epithelial cells,

reducing viral spread in the respiratory tract. Oseltamivir is the most widely prescribed neuraminidase inhibitor globally. Meta-analyses of randomised controlled trials (RCTs) reported that oseltamivir treatment of uncomplicated laboratory-confirmed influenza started within 2 days of symptom onset reduces illness duration by approximately 18 h overall and 30 h in those without asthma, and risk of otitis media by 34% versus placebo, but increases vomiting in children,[81] and in adults when started within 36 h of symptom onset, reduces the median time to alleviation of symptoms by 25 h, reduces by 44% the risk of lower-respiratory-tract complications occurring more than 48 h after starting oseltamivir treatment that requires antibiotic treatment, and reduces the risk of hospital admission for any cause by 63%, but increases the risk of nausea and vomiting versus placebo.[82]

A meta-analysis of individual participants' data reported that neuraminidase inhibitor treatment of influenza in outpatients at high risk of complications reduced the odds of hospital admission by 76% versus no treatment.[83] Oseltamivir is recommended for treatment of outpatients at higher risk for complications or who have progressive disease, even if more than 2 days from illness onset.[26] One dose of the polymerase inhibitor, baloxavir, a cap-dependent endonuclease inhibitor, blocks viral replication and rapidly reduces upper-respiratory-tract viral concentrations when started within 2 days of illness onset, has similar clinical benefit to 5 days of oseltamivir treatment, including in adolescents and adults at increased risk of complications, has greater efficacy against influenza B than oseltamivir, and can reduce the risk of some complications.[84,85] Baloxavir is not recommended in pregnant people because of the scarcity of efficacy and safety data, whereas abundant safety data exist for oseltamivir in pregnancy.[86] Meta-analyses have reported that treatment with oseltamivir, zanamivir, peramivir, or baloxavir is associated with shorter time to alleviation of symptoms of uncomplicated influenza versus placebo,[87] and treatment with neuraminidase inhibitors (primarily oseltamivir) or baloxavir significantly reduces antibiotic prescriptions compared with placebo.[88] Antiviral drug exposure can result in a low frequency of emergence of influenza viral variants with reduced drug susceptibility. Emergence of oseltamivir resistance with treatment is generally uncommon in immunocompetent patients, appears to occur slightly more frequently in influenza A(H1N1)pdm09 virus infections than A(H3N2) virus infections,[89] but is higher for patients who are severely immunocompromised and who have prolonged influenza viral replication,[25] and transmission to close contacts is possible.[90] Resistance to baloxavir can emerge rapidly at low frequency, more commonly with treatment of A(H3N2) virus infections than A(H1N1)pdm09 virus infections,[82] but is more frequent in young children.[91] Infrequent transmission of baloxavir-resistant virus to household contacts has been reported.[92,93] Combination therapy using antivirals with different mechanisms of action in people who are immunocompromised could reduce the risk of emergence of resistant viruses, but results from RCTs are not available.

The adamantane antivirals amantadine and rimantadine that block the M2-channel of influenza A viruses, with no activity against influenza B viruses, are not recommended because of the high prevalence of resistance to these drugs among circulating influenza A viruses.[26] Other antivirals with activity against influenza A and B viruses include the haemagglutinin inhibitor umifenovir, approved in Russia and China, which has shown clinical benefit in an RCT in adult outpatients, and the polymerase inhibitor favipiravir, approved in Japan for treatment of novel or re-emerging influenza viruses.[94,95] Other agents with antiviral activity against influenza viruses, including immunotherapeutics, are under investigation and have been reviewed elsewhere.[95]

Although there are no completed fully enrolled RCTs of antivirals versus placebo for treatment of patients hospitalised with influenza, prompt empiric oseltamivir treatment has been recommended in many countries on the basis of potential delays in receiving results of influenza testing at clinical laboratories and observational studies that reported survival benefit (18% reduction in mortality) of neuraminidase inhibitor treatment versus no treatment, and reduced hospital duration (19% reduction and median 1·1 day reduction) with neuraminidase inhibitor treatment started promptly after hospital admission in adults, compared with later initiation or no treatment.[96–98] An observational study reported that neuraminidase inhibitor treatment (nearly all oseltamivir) started within 2 days of illness onset in children hospitalised with influenza and underlying medical conditions or in those admitted to the ICU was associated with shorter length of stay compared to later initiation or no treatment.[99] An RCT of antiviral treatment versus placebo would clarify the role of antivirals in patients hospitalised with influenza. One RCT of combination neuraminidase inhibitor (primarily oseltamivir) and baloxavir treatment of patients hospitalised with influenza aged 12 years or older did not find clinical benefit compared with neuraminidase inhibitor and placebo, but the addition of baloxavir significantly reduced influenza viral RNA concentrations,[100] and has implications for infection prevention and control measures.

Clinical management

Management of influenza in patients who are not admitted to hospital consists of starting antiviral treatment as soon as possible after illness onset, especially in people at high risk for complications or those with progressive disease, and supportive care.[26,101] In addition to prompt initiation of antiviral treatment and implementation of infection prevention-and-control measures to prevent health-care-associated influenza, clinical management of influenza in patients who are hospitalised includes supportive care of complications (eg, antibiotics for bacterial co-infection or low-flow supplemental oxygen)

and exacerbation of chronic medical conditions, and providing critical care and advanced organ support (eg, high-flow supplemental oxygen, non-invasive or invasive mechanical ventilation, renal replacement therapy, vasopressors, and extracorporeal membrane oxygenation for refractory hypoxaemia). The utility of prognostic scoring systems, such as those developed for community-acquired pneumonia, to inform management of severe influenza is unclear. The value of biomarkers, including markers of inflammation, to inform clinical management and prognosis of severe influenza also needs to be defined.

The role of immunomodulatory therapy in severe influenza complications is unclear. Observational studies have reported that corticosteroids might prolong influenza viral replication and viral RNA detection.[26] A meta-analysis of 21 observational studies reported that corticosteroid treatment of influenza was associated with increased mortality, but risk-of-bias assessment was consistent with potential confounding by indication.[102] Another meta-analysis of a small subgroup from one RCT and 18 observational studies reported that corticosteroid treatment of influenza-related pneumonia or ARDS was associated with significantly higher mortality, but among patients from studies with adjusted analyses, there was no significant difference in mortality between corticosteroid recipients and controls.[103] Both meta-analyses reported that corticosteroid treatment of influenza increased the risk of hospital-acquired infections. One single centre, open-label RCT in adults hospitalised with influenza reported that clarithromycin, naproxen, and oseltamivir significantly reduced length of hospital stay, and 30-day and 60-day mortality compared with oseltamivir and placebo.[104] RCTs of low-dose or moderate-dose corticosteroids or other immunomodulators are needed to inform their roles in treating severe influenza complications.

Prevention and control interventions

Community settings

Before the COVID-19 pandemic, evidence for the community effectiveness of non-pharmaceutical interventions (NPIs) for prevention and control of influenza was scarce.[105,106] After emergence of SARS-CoV-2, cocirculation with influenza viruses was observed in some countries, and some co-infections occurred with these viruses.[59] From the early spring of 2020 to late 2021, influenza activity declined substantially and generally remained low after implementation of NPIs and behavioural changes (eg, school closures with online instruction, workplace closures and telework, wearing face masks in public settings, physical distancing, indoor dining restrictions, travel restrictions, isolation of people who were ill and the quarantine of those who were exposed, and border control measures) to control the spread of SARS-CoV-2.[107–110] Increases in influenza activity were observed after relaxation of control measures in some southeast Asian countries in 2020,[111] and influenza activity increased in late 2021 as NPIs were reduced.[112]

Health-care settings

Engineering and environmental controls can reduce exposures from infectious respiratory aerosols or contaminated surfaces and inanimate objects to health-care personnel (HCP) and patients.[113] The Centers for Disease Control and Prevention (CDC) recommends a minimum room ventilation rate of six air changes per hour in an existing facility and a higher ventilation of 12 air changes per hour for new or renovated construction are required to prevent room contamination, especially when managing patients receiving mechanical ventilation and during aerosol-generating procedures.[113]

Source control with a face mask is recommended for outpatients and patients with acute respiratory symptoms in emergency departments, including suspected seasonal influenza, ideally with placement in a single patient isolation room for evaluation. Use of influenza PoC assays can inform decisions to initiate antiviral treatment and infection prevention-and-control measures. If single isolation rooms are not available, patients with influenza who are hospitalised can be grouped together (cohorting). Standard and droplet precautions (face mask, gown, gloves, and hand hygiene before and after patient contact) for HCP are recommended for routine management of patients with suspected or confirmed seasonal influenza.[113] A cluster randomised, pragmatic, effectiveness study among outpatient HCP found no significant difference in laboratory-confirmed influenza between people who wore N95 respirators versus medical masks.[114] The risk of influenza virus infection of the upper respiratory tract from virus-laden droplets deposited on conjunctivae and spread through the nasolacrimal duct is unknown, and whether routine eye protection for HCP is indicated needs to be defined. The COVID-19 pandemic has highlighted the absence of consensus on what constitutes an aerosol-generating procedure, including which procedures present high risk of SARS-CoV-2 transmission to HCP.[115,116] Further studies are also needed to better define aerosol-generating procedures that present a risk of influenza virus transmission. Current CDC guidance recommends that when performing aerosol-generating procedures (eg, bronchoscopy, sputum induction, elective intubation, and extubation) on patients with severe influenza, ideally the patient should be placed in a negative-pressure airborne isolation room, and HCP should wear a fitted N95 filtering-facepiece respirator or equivalent respiratory protection with eye protection (face shield or goggles).[113] Influenza viral RNA has been detected infrequently in the stool of patients with seasonal influenza, but virus has very rarely been isolated from faecal specimens;[117] the risk of transmission from stool is unknown but likely to be very low. Similarly, influenza viral RNA has been detected infrequently in blood in patients with seasonal influenza, particularly in those who are critically ill,[118] but has rarely ever been isolated from blood.[119] The risk of transmission of influenza viruses from respiratory secretions, fomites, stool, or blood is unknown but is likely to be very low.

	Haemagglutinin concentration per virus antigen	Administration	Manufacturing process	Approved age group recommendations*
Inactivated, split or subunit, at standard dose	7·5 µg or 15 µg (varies by manufacturer and country)	Intramuscular	Egg-grown viruses; inactivated	6 months to 35 months (two doses recommended for previously unvaccinated children)
Inactivated, split or subunit, at standard dose	15 µg	Intramuscular	Egg-grown viruses; inactivated (aluminum phosphate adjuvant might be used in some countries)	≥6 months (two doses recommended for previously unvaccinated children aged 6 months to 8 years)
Inactivated, split or subunit, at standard dose	15 µg	Intramuscular	Tissue cell-culture grown; inactivated	≥2 years; ≥9 years in some countries (two doses recommended for previously unvaccinated children aged 6 months to 8 years)
Live attenuated, at standard dose	15 µg	Intranasal	Egg-grown viruses that replicate in nasal passages, but do not replicate at internal body temperature (cold adapted), and express virus antigens	2 years to 49 years (for non-pregnant, non-high-risk conditions; 2 doses recommended for previously unvaccinated children aged 6 months to 8 years)
Recombinant	45 µg	Intramuscular	Recombinant haemagglutinin DNA expressed in insect-cell culture and purified	≥18 years
Inactivated, split or subunit, at standard dose, and adjuvanted	15 µg	Intramuscular	Egg-grown viruses; inactivated; administered with MF59 adjuvant	≥65 years
Inactivated, split or subunit, at high dose	60 µg	Intramuscular	Egg-grown viruses; inactivated	≥65 years

Adapted from Grohskopf and colleagues.[120] Vaccines might be available in trivalent or more commonly quadrivalent formulations depending on country and manufacturer. Trivalent vaccines contain antigens for three virus strains; one influenza A(H1N1)pdm09 strain, one influenza A(H3N2) strain, and either one influenza B or Yamagata lineage or one B/Victoria lineage. Quadrivalent vaccines contain antigens for one representative of both type B lineages in addition to the A(H1N1)pdm09 and A(H3N2) virus strains. *Check national guidance for differences in recommended age groups.

Table 4: **Characteristics of generally available seasonal influenza vaccines**

Nevertheless, contact precautions and hand hygiene are indicated for HCP caring for patients with influenza; standard cleaning and disinfection of surfaces in health-care settings, including areas in which aerosol-generating procedures are done, are thought to be adequate for influenza-virus environmental control in health-care settings.[113]

When health-care-associated influenza is suspected or confirmed, particularly in congregate settings such as long-term-care facilities, implementation of a bundle of NPIs is recommended, as is influenza vaccination of unvaccinated people, antiviral treatment of people who are symptomatic, and antiviral chemoprophylaxis of exposed individuals.[26] Both oseltamivir and baloxavir can be used for prophylaxis after exposure, but should be administered within 1–2 days of exposure to a close contact with influenza.[26,101]

Influenza vaccines and vaccine effectiveness

Annual influenza vaccination is recommended because of waning immunity over time and antigenic drift among circulating influenza viruses that requires annual updating of vaccine antigens. Most influenza vaccines used worldwide are manufactured using influenza viruses propagated in eggs and formalin inactivated, with antigens presented as split or subunit, without adjuvant (table 4).[121] Standardisation is based on haemagglutinin content, with most vaccines containing 15 µg of each haemagglutinin antigen. Most available vaccines worldwide are quadrivalent, containing an A(H3N2) and an A(H1N1)pdm09 virus strain, and a representative of each of the Victoria and Yamagata lineages of influenza B viruses, or trivalent in some countries, containing the two influenza A virus strains and one influenza B virus lineage.

Because immunogenicity of standard dose vaccines is reduced in older adults, vaccines with higher antigen content (eg, a recombinant vaccine containing three times [45 µg] the antigen content for each component or a high-dose vaccine containing four times [60 µg] the antigen content for each component) or an adjuvanted vaccine with standard amounts of egg-derived antigens[120] are available in some countries for use in this population. Given that adaptation of influenza viruses to eggs for vaccine production might render the vaccine less protective,[122] vaccines are available that are either propagated in cell culture or produced by molecular technology from genetic sequences and manufactured using insect-cell culture. Live attenuated influenza vaccines have been available since 2003 in an increasing number of countries and are licensed in the USA for non-pregnant people aged 2–49 years without chronic medical conditions,[120] but are mainly used in children in most countries and represent only approximately 5% of influenza vaccines produced worldwide.[121]

The vaccine viral antigens are updated regularly because of antigenic drift among circulating influenza viruses. WHO makes recommendations on vaccine composition twice per year for the northern and southern hemispheres following review of antigenic and molecular characteristics of circulating strains worldwide (appendix p 1). Recommendations for vaccine use vary greatly internationally. In the USA, annual influenza vaccination is recommended for all people aged 6 months and older, and vaccine coverage is approximately 50–60% among children

and adults. However, disparities in influenza vaccination exist in the USA, with the lowest vaccination coverage among people younger than 18 years in Black children, and among people aged 18 years or older in Black and Hispanic adults.[123–125] HCP and older adults are the priority groups for annual vaccination in many countries. Attempts have been made to modify outbreaks by vaccinating children to protect others, but evidence for indirect protection might be difficult to identify or modest.[126–128] WHO has identified pregnant people as a priority target for vaccination with the goal of protecting them and their newborn children on the basis of RCTs.[127] Influenza vaccines have shown safety in pregnant and non-pregnant people,[129,130] especially in terms of the many millions of vaccine doses administered worldwide each year. Influenza vaccine can be coadministered with COVID-19 vaccine.[120]

Influenza vaccine effectiveness is typically estimated by comparing vaccine history in those meeting an influenza case definition who test positive or negative for influenza (test-negative design).[131] Influenza vaccine effectiveness can vary depending upon the antigenic match between circulating influenza virus strains and vaccine components, time since vaccination because of waning immunity, and host factors such as age, immune function, earlier exposure to influenza viruses, and vaccination history.[132–134] Vaccine effectiveness might also be reduced by molecular changes arising from egg adaption for vaccines that use viruses grown in embryonated eggs, such as in the influenza A(H3N2) vaccine component.[122] The test-negative design has shown that the A(H1N1)pdm and type B components are generally more protective than A(H3N2), particularly in older adults, but can still provide moderate protection against influenza-related complications requiring hospitalisation in children and adults.[135,136] Influenza vaccination of people with cardiovascular disease can reduce mortality and major adverse cardiovascular events.[137] During 2004–20, influenza vaccine effectiveness against medically attended influenza among outpatients in the USA ranged from 10% to 60% and varied by antigenic match to circulating virus strains.[138]

Major efforts are underway to develop more effective influenza vaccines of greater breadth and duration of protection. The goal is a vaccine that will provide extended immune protection against pandemic viruses or antigenically drifted viruses causing epidemics, and without requiring annual vaccination, often referred to as a universal vaccine.[139] The term supraseasonal has been used for a more broadly protective vaccine for seasonal influenza. Strategies being studied include stimulating antibodies directed against the haemagglutinin stem or other conserved epitopes, and standardising neuraminidase content for improved response or more reliance on adjuvants.[140] A standardised human influenza-virus challenge model can contribute insights into the effectiveness of more broadly protective vaccines.[141,142] The mRNA technology used for some COVID-19 vaccines was originally developed for influenza vaccines and both mRNA influenza vaccines and combined mRNA COVID-19-influenza vaccines are under development.[143] In addition, an adjuvanted nanoparticle vaccine is under development for older individuals.[144] Nevertheless, even with the modest vaccine effectiveness of currently available influenza vaccines against medically attended influenza, vaccination is effective in preventing some severe influenza outcomes, such as ICU admission (26% risk reduction) and mortality (31% risk reduction) among adults with influenza-associated hospital admission.[145,146]

Lessons from COVID-19 for prevention and control of influenza

The effect of community-wide and national use of NPIs to control SARS-CoV-2 transmission on reducing influenza virus circulation suggests that such measures combined with influenza vaccination could be important public health tools during severe influenza epidemics and pandemics. Supplies of personal protective equipment must be ensured for HCP. Inequities in the global availability of COVID-19 vaccines highlight the need to expand efforts to increase influenza vaccine manufacturing capacity worldwide and increase influenza vaccine access and use in low-income and middle-income countries,[147] which will also improve pandemic vaccine response.

Regional and multinational clinical research networks were invaluable in rapidly implementing adaptive clinical trials to identify therapeutics that led to significant improvements in the care and survival of patients hospitalised with COVID-19,[148–150] and can be used to identify interventions that improve care for patients with influenza.[151] Oxygen shortages for patients with COVID-19 highlighted the urgency to increase capacity and expand access to oxygen and monitoring for patients with hypoxaemia worldwide. Surges of patients severely ill with COVID-19 overburdened hospitals in low-resource and high-resource settings with resultant patient harm,[152] emphasising that more efforts are needed to prevent illness or avert progression to severe disease during severe influenza epidemics and pandemics, and there is a need to increase critical care capacity worldwide. Wider global availability of highly sensitive influenza assays and effective, affordable oral antiviral medications can facilitate prompt influenza diagnosis and early initiation of treatment to avert severe disease. Novel influenza A virus infections of humans present ongoing pandemic threats (appendix pp 1–2, 11).

Conclusions

Influenza vaccines with much higher effectiveness are greatly needed, especially for older adults, ideally conferring broader and longer duration of protective immunity than current vaccines. Many gaps and questions in the clinical management of influenza need to be addressed, particularly to optimise supportive care of patients who are hospitalised.[153,154] Prospective observational

studies with serial respiratory sampling and integrated analyses of virological, genetic sequencing, clinical, immunological, transcriptomics, proteomics, and host genomics can yield insights for targeting therapies in select patients with influenza who are hospitalised. Priorities for multinational clinical research networks are clinical trials of immunomodulators (eg, IL-6 receptor blockers and low-to-moderate dose corticosteroids) and combined antiviral and immunomodulator treatments in patients with severe influenza (appendix p 12). Although more effective therapeutics and targeted interventions are needed, a logistical challenge in almost all countries is how to implement prompt influenza diagnostic testing and initiation of treatment soon after illness onset with available antivirals, particularly in people at high risk for complications, for the greatest clinical benefit.

Contributors

All authors did literature reviews for the sections they drafted. TMU drafted the Summary and Introduction, and the sections on Transmission dynamics and modalities, Epidemiology and disease burden, Treatment, Prevention and control interventions community settings, and Lessons from COVID-19 for prevention and control of influenza, and contributed to the tables and edited all sections. DSH drafted the sections on Clinical spectrum and clinical complications, Clinical management, and Prevention and control interventions health-care settings, and contributed to the figures. DEW drafted the Virology and Pathogenesis sections. MZ drafted the sections on Influenza surveillance and Diagnostic testing, and contributed to the figures. ASM drafted the section on Influenza vaccines and vaccine effectiveness, contributed to the tables, and coedited all sections and tables. All authors approved of the final draft.

Declaration of interests

DSH reports grant support unrelated to contributions to the Clinical spectrum and clinical complications, Clinical management, and Prevention and control interventions health-care settings sections, and, outside the submitted work support, from F Hoffmann-La Roche for a research nurse to enrol participants in a phase 3, randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of baloxavir marboxil in combination with standard-of-care neuraminidase inhibitor in hospitalised patients with severe influenza. DEW reports research unit support (CRADA) from Seqirus for evaluation of virus isolation and propagation of viruses for the implementation of cell-based vaccines (US$200 000 per year) unrelated to contributions to the virology and pathogenesis sections and outside the submitted work. MZ reports being a member of the WHO Strategic Advisory Group of Experts on Immunization, the J Craig Venter Institute, and the UK New and Emerging Respiratory Virus Threats Advisory Group, and is Chair of the International Society of Influenza and Respiratory Viruses, unrelated to contributions to the influenza surveillance and diagnosis sections and outside the submitted work. ASM reports serving on a Roche advisory board unrelated to the contributions to the Influenza vaccines and vaccine effectiveness sections and outside the submitted work. TMU declares no competing interests. The views expressed are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the UK Health Security Agency.

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