Influenza infection

The right clinical information, right where it's needed
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td>3</td>
</tr>
<tr>
<td><strong>Basics</strong></td>
<td>4</td>
</tr>
<tr>
<td>Definition</td>
<td>4</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>4</td>
</tr>
<tr>
<td>Aetiology</td>
<td>4</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>5</td>
</tr>
<tr>
<td>Classification</td>
<td>5</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>6</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>6</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>7</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>8</td>
</tr>
<tr>
<td>Case history</td>
<td>8</td>
</tr>
<tr>
<td>Step-by-step diagnostic approach</td>
<td>8</td>
</tr>
<tr>
<td>Risk factors</td>
<td>10</td>
</tr>
<tr>
<td>History &amp; examination factors</td>
<td>12</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>13</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>16</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>18</td>
</tr>
<tr>
<td>Step-by-step treatment approach</td>
<td>18</td>
</tr>
<tr>
<td>Treatment details overview</td>
<td>20</td>
</tr>
<tr>
<td>Treatment options</td>
<td>22</td>
</tr>
<tr>
<td>Emerging</td>
<td>34</td>
</tr>
<tr>
<td><strong>Follow up</strong></td>
<td>36</td>
</tr>
<tr>
<td>Recommendations</td>
<td>36</td>
</tr>
<tr>
<td>Complications</td>
<td>37</td>
</tr>
<tr>
<td>Prognosis</td>
<td>39</td>
</tr>
<tr>
<td><strong>Guidelines</strong></td>
<td>40</td>
</tr>
<tr>
<td>Diagnostic guidelines</td>
<td>40</td>
</tr>
<tr>
<td>Treatment guidelines</td>
<td>40</td>
</tr>
<tr>
<td><strong>Online resources</strong></td>
<td>43</td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>44</td>
</tr>
<tr>
<td><strong>Disclaimer</strong></td>
<td>56</td>
</tr>
</tbody>
</table>
Characterised by upper and lower respiratory tract symptoms of rhinorrhoea, cough, fever, chills, headache, and myalgia.

Typically presents in winter season.

Can occur in local community outbreaks, epidemics, and, rarely, pandemics.

Vaccination for prevention is available.
Influenza infection

Basics

Definition

Acute respiratory tract infection typically caused by seasonal influenza A or B virus. The virus is transmitted by inhalation of infected respiratory secretions that have been aerosolised through coughing, sneezing, or talking.[1]

Epidemiology

The incidence of seasonal influenza infection is difficult to determine, as not everyone with influenza will seek medical attention, and not everyone with influenza-like illness will have influenza infection; diagnosis may be made clinically without laboratory confirmation. Additionally, incidence varies each year, with antigenic change in the viruses meaning that there is no incremental protection from previous immunisations. Overall, it is estimated to affect 20% of children and 5% of adults worldwide each year.[5] Studies in children report an average annual incidence of 4.6% over a 5-year period in children up to 19 years of age. Over a 25-year period in the US, the incidence was 9.5% of children <5 years of age.[5] In the northern hemisphere, seasonal influenza activity peaks between late December and early March, and in the southern hemisphere it peaks between May and September.

There have been four influenza pandemics since 1918, with the most recent being the Influenza A (H1N1) ‘swine flu’ epidemic in April 2009. In 1957 and 1968, both pandemics were as a result of novel strains of both human and avian influenza. However, the pandemic of 2009 was as a result of a novel gene rearrangement of human, avian, and swine influenza.[6]

In 2017, a fast-mutating strain of influenza A (H3N2) was reported in Australia, which saw the highest number of cases since the 2009 pandemic.[7] In the 2017-2018 season, influenza activity in the US is also reported to have reached its highest level since the 2009 H1N1 pandemic. [CDC: FluView - weekly influenza surveillance report]

In 2005, researchers at the Centers for Disease Control and Prevention (CDC) successfully reconstructed the 1918 Influenza A (H1N1) virus, enabling better a understanding of its virulence. It is highly unlikely that the 1918 virus would re-emerge from a natural source and, even if it did, residual immunity means it would no longer be considered a novel strain. If it was ever isolated outside of a laboratory, current treatments (such as the antivirals rimantadine and oseltamivir) would likely be effective and there would be the potential for vaccines, as those containing the 1918 haemagglutinin protein have been shown to be protective in mice.[8]

Aetiology

Seasonal influenza virus is a member of the orthomyxovirus family. It has a segmented, single-stranded RNA genome that can be classified into influenza A, B, and C based on antigenic differences. The RNA codes for five structural proteins and three non-structural proteins. Protein M and nucleoprotein NP elements are used to classify the virus into the types A, B, and C. Other elements of the virus structure, haemagglutinin (H antigen) and neuraminidase (N antigen), are important in the pathogenesis of the disease. The H antigen is required for binding and entry of the virus into the cell. The N antigen helps the mature virus to escape from the cell.

Seasonal influenza virus types A and B are also divided into a number of subtypes. These subtypes are defined by the H and N antigens present on the virus. There are three antigenic subtypes of H antigen
Influenza infection

Basics

(H1, H2, and H3) and two antigenic subtypes of N antigen (N1 and N2), allowing for a number of different combinations. Antibodies to one subtype of H or N antigen do not react with another type of the H or N antigen.

Influenza C is not associated with epidemics or pandemics and causes mild disease. Influenza A is responsible for frequent (usually annual) local outbreaks or larger epidemics of varying intensity every 2-3 years, or occasional pandemics. Influenza B causes outbreaks approximately every 4 years, with usually milder disease than influenza A.[9] Epidemics usually occur from late autumn to early spring.

Small point mutations in the proteins that make up the influenza virus cause antigenic drift, and this is the reason why new vaccines are required each influenza season. Larger changes that result in new haemagglutinin or neuraminidase proteins cause antigenic shifts and may result in pandemics. Special terminology used when discussing an influenza virus includes the type of influenza virus, the place it was first located, and the year it was first discovered.

Pathophysiology

Seasonal influenza virus is transmitted through infected respiratory droplets that are aerosolised by coughing, sneezing, or talking. Less commonly, contact with fomites may cause transmission.[5]

The virus binds to and enters the tracheobronchial ciliated epithelium by utilising the viral surface haemagglutinin (H antigen). Viral replication then occurs. Peak viral shedding occurs in the first 48 to 72 hours of exposure to the virus, then declines and becomes undetectable within 10 days. Children and immunocompromised people may shed virus for several weeks.[10]

Classification

Seasonal influenza virus types

Influenza virus is classified into influenza A, B, and C based on antigenic differences. Other elements of the virus structure are haemagglutinin (H antigen) and neuraminidase (N antigen).

Influenza virus types A and B are divided into several subtypes. These subtypes are defined by the H and N antigens present on the virus. There are three antigenic subtypes of H antigen (H1, H2, and H3) and two antigenic subtypes of N antigen (N1 and N2), allowing for several different combinations.

Influenza C is not associated with epidemics or pandemics and causes mild disease.
Influenza infection
PREVENTION

Primary prevention

Primary prevention for influenza is provided by the influenza vaccine.[38] [39] [40] [41] [42] [43] [44] [45] International guidelines vary in their recommendations of who should receive vaccination. The US Centers for Disease Control and Prevention (CDC) currently recommends influenza vaccine for all people aged ≥6 months who do not have contraindications to vaccination.[46] [CDC: influenza (flu)] For 2019-2020, the CDC Advisory Committee on Immunization Practices (ACIP) recommend that any licensed, age-appropriate influenza vaccine may be used, including the live attenuated vaccine where it is appropriate.[46] The American Academy of Pediatrics (AAP) also now states that both inactivated influenza and live attenuated influenza vaccine are options for children, with no preference (unless contraindicated).[14] Trials are under way for use of the influenza vaccine in young infants (<6 months of age).[47] Children aged 6 months to 8 years require two doses of influenza vaccine (administered ≥4 weeks apart) during their first season of vaccination to optimise response.[46] The ACIP recommends that children aged 6 months to 8 years who have previously received ≥2 doses of trivalent or quadrivalent influenza vaccine before July 1, 2019, require only one dose for 2019-2020.[46] Beginning at age 9 years, only one annual dose is recommended.[48] Pregnant women may receive any licensed, recommended, age-appropriate inactivated vaccine; the live attenuated influenza vaccine should not be used during pregnancy.[46] Influenza vaccination during pregnancy is not associated with an increased risk of infant hospitalisation or death in the first 6 months of life,[49] and may help prevent influenza hospitalisations among pregnant women.[50] Additionally, influenza vaccination during pregnancy results in antibody development that can protect infants in the first few months of life.[51] Other international guidelines recommend vaccination for high-risk groups. Local guidelines should be consulted and followed.

For the 2019-2020 (northern hemisphere) season, the World Health Organization recommends that quadrivalent vaccines contain an A/Brisbane/02/2018 (H1N1)pdm09-like virus, an A/Kansas/14/2017 (H3N2)-like virus, a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage), and a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage). The influenza B component of trivalent vaccines should be a B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage.[52]

In the US, the AAP recommends all children with egg allergy of any severity can receive either an inactivated influenza vaccine or live attenuated influenza vaccine without any additional precautions beyond those recommended for any vaccine.[14] The ACIP recommends the following:[46] [53]

- People with a history of egg allergy who have experienced only hives after exposure to egg should receive influenza vaccine (any licensed, recommended, age-appropriate influenza vaccine).
- People who have reported reactions to egg (involving such symptoms as angio-oedema, respiratory distress, lightheadedness, or recurrent emesis) or who required epinephrine (adrenaline) or another emergency medical intervention may receive influenza vaccine (any licensed, recommended, age-appropriate influenza vaccine). The vaccine should given by a physician with experience in the recognition and management of severe allergic conditions.
- People who are able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be allergic. Egg-allergic people might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy. Egg allergy can be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus skin and/or blood testing for immunoglobulin E directed against egg proteins.
- For people with no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained before vaccination.
- A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

Regardless of allergy history, all vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available.
Influenza infection

Prevention

Administering the vaccine by a two-step approach and skin testing with vaccine are not necessary.[54] A trivalent vaccine made using an insect virus expression system and recombinant DNA technology is now available for adults aged 18 years or older. Unlike other vaccines, this vaccine does not use the influenza virus or eggs in the manufacturing process. A cell-based quadrivalent vaccine is available in the US for people aged ≥4 years, and in Europe for people aged ≥9 years. The cell-based quadrivalent vaccine is made using influenza viruses grown in cultured cells of mammalian origin instead of hen's eggs.[55] [56]

Vaccine effectiveness may vary according to the age of the recipient, the level of pre-existing immunity, and correctly predicting the specific circulating strains of virus.[57] [40] [41] [42] [43] [58] [59] [60] [61] [62] [63] [64] [65]

Vaccine efficacy in older people:

- Most influenza-associated deaths occur in the older population (aged ≥65 years).[66] [67] [68] A systematic review found that benefits of vaccination were more evident on health-related outcomes of residents in long-term care facilities than in healthy older individuals in the community.[69] A pooled cohort study published after the meta-analyses demonstrated a significant reduction in mortality in vaccinated older individuals (1.0% versus 1.6% in unvaccinated individuals).[67] The mortality benefit in older patients is increased with annual vaccination.[70] High-dose vaccination and boosting low titres midseason may be of benefit in older people.[71] [72] [73] [74] [75]
- Any licensed, age-appropriate vaccine may be used.[46]

Guillain-Barre syndrome (GBS) risk:

- GBS is an acute autoimmune disorder of peripheral nerves that develops in susceptible individuals after infection and, in rare cases, after immunisation. In the US, an increased risk of GBS was associated with the 1976 swine influenza vaccine (swine-origin influenza A H1N1 subtype A/ NJ/76).[76] The number of reports of influenza-vaccine-associated GBS to the national Vaccine Adverse Event Reporting System increased from 37 in 1992-1993 to 74 in 1993-1994. Studies of these cases showed that for the two seasons combined, the adjusted relative risk of 1.7 suggests slightly more than 1 additional case of GBS per million people vaccinated against influenza.[77] This risk seems to be substantially less than the overall health risk posed by naturally occurring influenza.
- A history of GBS within 6 weeks following receipt of influenza vaccine is a precaution for the use of influenza vaccine because of the risk of recurrent GBS. Risks and benefits of vaccination need to be considered in these instances.[46]

Secondary prevention

Both oseltamivir and zanamivir have been shown to be effective as prophylaxis against infection when given early after exposure to an infected individual.[135] Antiviral prophylaxis after exposure to an infected individual is reserved for at-risk populations.[109] [110] Findings from a meta-analysis showed that oseltamivir modestly reduces time to clinical symptom alleviation in adults with influenza, but increased the incidence of nausea and vomiting.[125]
Case history

Case history #1

A 30-year-old woman presents in the winter months with a 2-day history of fever, cough, headache, and generalised weakness. She was in her usual state of health before an abrupt onset of these symptoms. A few viral illnesses have affected her during the current winter, but not to this severity. She says she has sick co-workers and did not receive the influenza vaccine this season.

Case history #2

A 12-month-old infant presents in the winter months to the paediatrician with a 2-day history of fever to 38.9°C (102°F), tachypnoea, conjunctival erythema, and nasal congestion with clear discharge. There has been an associated loss of appetite, with one episode of emesis. Influenza has been reported recently in the locality. The parents are concerned that the child was not vaccinated, due to a known history of severe egg allergy.

Other presentations

Seasonal influenza may present rarely with an afebrile upper respiratory tract illness more typical of a common cold, or it may present predominantly with fever and myalgia, with few respiratory symptoms. Patients in high-risk populations (e.g., those with chronic cardiac or pulmonary conditions, diabetes mellitus, renal disease, haemoglobinopathy, immunosuppression, residence in chronic care facilities, age >50 years, or third trimester of pregnancy) may present with an established primary viral or secondary bacterial pneumonia. Characteristic features of primary viral pneumonia are persisting or worsening course of fever, with dyspnoea or other respiratory distress. Secondary bacterial pneumonia should be suspected if there is an initial improvement in symptoms followed by a relapse of fever with productive cough and shortness of breath. A chest x-ray confirms pulmonary infiltrates.

Step-by-step diagnostic approach

Influenza occurs in outbreaks mainly from December to March in the northern hemisphere and between May and September in the southern hemisphere. Knowledge of local community disease activity is important when assessing the likelihood that a patient has influenza. The US Centers for Disease Control and Prevention publishes a weekly influenza surveillance report for the US, [CDC: FluView - weekly influenza surveillance report] and the World Health Organization also tracks and reports incidence rates of influenza. [WHO: influenza update]

Diagnosis is usually made clinically during an outbreak in the community. Patients at high risk of developing complications, including those with a history of chronic lung, heart, or renal disease, infants and young children, and older adults, require special attention. Testing for influenza should be done if it will influence the decision to begin antiviral therapy, to order additional diagnostic tests, to institute infection control measures, and for community surveillance of influenza circulation.
History and examination

Influenza presents most commonly as an acute respiratory illness during the winter season. After an incubation period of approximately 2 days, there is an abrupt onset of high fever, chills, headache, and myalgia. These systemic symptoms may be associated with upper and lower respiratory tract symptoms similar to a common cold, such as cough and sore throat.[79] Viral shedding in influenza peaks within 48 hours of the illness, and most uncomplicated cases resolve within 1 week.[80] Influenza does not present commonly with primary gastrointestinal symptoms such as nausea and vomiting, except in the paediatric population. Diarrhoea is rare with influenza and would suggest a viral gastroenteritis, commonly referred to as stomach flu.

During a known influenza outbreak, any person with acute fever and respiratory symptoms should be considered to possibly have influenza. However, if the person has been exposed to influenza or a situation where influenza may be spread quickly (e.g., international travel, cruise ships), the diagnosis of influenza should be considered at any time of the year.

Although there are no clear pathognomonic features of influenza, it affects the upper and lower respiratory tract in association with systemic symptoms. Fever, headache, myalgia, and fatigue are often associated with upper respiratory tract symptoms such as sore throat and lower respiratory symptoms of cough.[81] Not all patients with influenza exhibit these symptoms, and those that do may not always have influenza. Overall, up to 85% of patients with influenza will exhibit clinical symptoms of influenza illness. Manifestations of influenza infection also depend on patient age and previous history of immunisation.[81][79]

With sporadic cases of influenza, it may be difficult to differentiate influenza clinically from infections caused by other respiratory viruses. In this scenario, influenza virus infection may account for only a small number of such cases. In a review of 497 episodes of upper respiratory tract infection in older patients living in the community during the winters of 1992 to 1994, a pathogen was identified in 43% of the cases. The most common pathogens were rhinoviruses (52%) and coronaviruses (26%); influenza A or B accounted for only 10%.[82]

Clinical findings are helpful, but do not confirm or exclude the diagnosis of influenza.[79] Examination may yield non-specific findings, since physical findings are generally few in cases of uncomplicated influenza. The patient may appear hot and flushed, and the oropharynx may demonstrate hyperaemia, with complaints of severe sore throat. Mild cervical lymphadenopathy may be present and is more frequent in younger patients.

Laboratory testing

The role of laboratory testing is to reduce the inappropriate use of antibiotics and to provide the option of using antiviral therapy. Diagnostic testing, in conjunction with surveillance, can also identify the predominant circulating types, subtypes, and strains of influenza.[78]

- Outpatient testing should be considered for any person who is at high risk of developing complications of influenza and who presents with an acute (up to 5 days) febrile illness.
- Outpatient immunocompromised people, older adults, and infants and children with febrile respiratory illness of any duration should be screened for influenza during an outbreak.
- Hospitalised patients with fever or who develop fever during hospitalisation for respiratory infection should be screened for influenza.
Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, PCR, and immunofluorescence assays.[78] [83] [84] [85]

Nasopharyngeal specimens are recommended for a respiratory specimen for viral isolation. They are more effective than throat swab specimens. Viral culture remains the definitive test, despite the availability of rapid diagnostic tests. It is not often used for initial clinical management as results may take up to 72 hours to be reported. Rather, it is used for confirming screening tests and for public health surveillance. Only culture isolates can provide specific information regarding circulating strains and subtypes of influenza viruses. Virus isolates may also provide information about the emergence of antiviral resistance and the development of novel influenza A subtypes that may potentially cause a pandemic.

In the outpatient setting a nasal swab, wash, or aspirate should be collected within the first 4 days of illness. Rapid influenza tests provide results within 30 minutes or less; viral culture provides results in 3 to 10 days. Rapid tests are approximately 70% sensitive and 90% specific for detecting influenza.

Routine serological testing for influenza requires paired acute and convalescent sera. It is not recommended for accurate clinical decision-making.

During outbreaks of influenza, respiratory samples should be tested by both rapid tests and viral culture. Viral culture is essential for determining the influenza A subtypes and influenza A and B strains causing illness, and for surveillance of new strains that may need to be included in the next year’s influenza vaccine. Viral culture can also help to identify other causes of illness.

**Pneumonia**

If a patient has an underlying chronic medical condition or falls into a high-risk category, viral or bacterial pneumonia should be considered. These patients will experience persistence of their symptoms beyond the usual time frame for resolution of uncomplicated influenza. There may be high fever, cough, and dyspnoea. If there is an exacerbation of fever and cough with purulent sputum, a secondary bacterial pneumonia is most likely. A chest x-ray confirms infiltrates.

**Diagnosis in children**

Signs and symptoms of upper and/or lower respiratory tract involvement are common, but influenza may present more variably in children, depending on age and previous exposure.

The typical symptoms of uncomplicated influenza virus infection are still often present and include the abrupt onset of fever, headache, myalgia, and malaise associated with manifestations of respiratory tract illness, such as cough, sore throat, and rhinitis.

However, young children frequently struggle to vocalise such symptoms as myalgia and headache. They may have higher fevers than adult patients, experience febrile seizures, and have more gastrointestinal complaints (e.g., nausea and vomiting, poor appetite).[86] [87] Respiratory symptoms may be less prominent in children at the onset of illness than in adolescents and adults.[86]

Clinical findings in children may include fever, tachypnoea, conjunctival erythema, nasal oedema and discharge, hyperaemia of oropharynx, and cervical adenopathy.[88]

**Risk factors**
Influenza infection

Diagnosis

Strong age ≥65 years

- Compared with young, healthy adults, people aged ≥65 years are at greater risk of serious complications from influenza, and are more likely to have comorbid conditions that may be exacerbated by influenza infection. It is estimated that 90% of seasonal influenza-related deaths and more than 60% of seasonal influenza-related hospitalisations in the US each year occur in people ≥65 years.[11] [12] Influenza can be a very serious disease when immune defences become weaker with age. This age also brings a greater likelihood of comorbid conditions that may be exacerbated with influenza infection.[13]

Age 6-59 months

- Although children with chronic medical conditions such as pulmonary, renal, or cardiac disease have a high risk of complications of influenza, otherwise healthy children are at risk simply because of their age. Children aged <5 years are more likely to be hospitalised than older children; those aged <2 years are at elevated risk of complications attributable to influenza.[14]

Chronic cardiovascular or respiratory conditions

- In patients with moderate or severe COPD, the presence of any virus in upper airway secretions is strongly associated with the development of COPD exacerbations. These data support the causative role of viruses in triggering COPD exacerbations in the community.[15] [16]
- In older populations, vaccination against influenza is associated with reductions in the risk of hospitalisation for heart disease, cerebrovascular disease, and pneumonia or influenza, as well as the risk of death from all causes during influenza seasons. These findings highlight the benefits of vaccination and support efforts to increase the rates of vaccination among older people.[16] [17] [18]

Chronic kidney disease (CKD)

- Patients with CKD are at increased risk of influenza complications.[13] Influenza vaccine is currently recommended for patients with CKD by the Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention.[19] In observational studies, influenza vaccination is associated with decreased risk of influenza-related hospitalisations, deaths, and physician visits.[20]

Diabetes

- People with diabetes are at greater risk of complications due to their underlying disease.[21] Diabetes confers a 5% to 12% increase in mortality from influenza infection, thought to be due to increased risk of metabolic disruption, ketoacidosis, impaired immune response, and increased carrier rates of staphylococci and streptococci.[22]

Haemoglobinopathy

- Haemoglobinopathies such as sickle cell disease involve abnormalities not just in red blood cells but also in vascular endothelium, white blood cell function, coagulation, and inflammatory response. Routine influenza vaccination is recommended for infection prevention.[23]

Immunocompromise

- Infection is the leading cause of morbidity and mortality in immunocompromised patients such as haematopoietic/solid organ transplant recipients and individuals with HIV.[24] [25] [26] Inactivated influenza virus vaccine is preferred over live virus vaccine for household members, healthcare workers, and others coming into close contact with severely immunosuppressed people requiring...
care in a protected environment. In one study, vaccination with a high-dose trivalent vaccine resulted in higher levels of seroprotection in people with HIV. Trivalent inactivated influenza vaccine is also immunogenic pregnant women with HIV. Inactivated vaccine should be used with caution in severely immunocompromised patients (e.g., patients receiving chemotherapy, radiation therapy, or other immunosuppressive therapy, including high-dose corticosteroids), as there may be a reduced response to vaccination. However, adjuvanted vaccine has been shown to be safe and immunogenic in the transplant population. Intranasal live-attenuated vaccine is contraindicated in immunosuppressed or immunocompromised patients.

**pregnancy**

- Immune, respiratory, and cardiovascular changes make pregnant women more prone to severe illness from influenza. Pregnant women with influenza have a greater risk of preterm labour and delivery. Trivalent inactivated influenza vaccine is immunogenic in both HIV-infected pregnant women and pregnant women who are not infected. With regard to safety, maternal influenza vaccination does not increase risk of congenital malformations.

**carers and household contacts of high-risk groups**

- The goal is to prevent transmission of the virus to a high-risk population.
- Inactivated influenza virus vaccine is preferred over live virus vaccine for household members, healthcare workers, and others coming into close contact with severely immunosuppressed people requiring care in a protected environment.

**healthcare workers**

- Healthcare workers play an important role in protecting public health. The Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention recommends that all healthcare workers receive an annual influenza vaccination to limit the spread of infection. Inactivated influenza virus vaccine is preferred over live virus vaccine for household members, healthcare workers, and others coming into close contact with severely immunosuppressed people requiring care in a protected environment.
- As a vaccinated healthcare worker, there is protection for family at home as well as patients at work from possible influenza transmission. Influenza outbreaks in hospitals and long-term care facilities have been attributed to low vaccination rates among healthcare professionals.

**History & examination factors**

**Key diagnostic factors**

**winter season (common)**

- Influenza tends to have a seasonal outbreak pattern, with epidemics usually occurring between late autumn and early spring.

**current influenza outbreak (common)**

- Suspicion for seasonal influenza should be high if there is a documented outbreak in the community. During the influenza season, the US Centers for Disease Control and Prevention publishes weekly updates online that summarise information about influenza activity. The WHO also tracks and reports incidence rates of influenza.  

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**Influenza infection**

**Diagnosis**

unvaccinated (common)

- Patients should be asked whether they receive the seasonal influenza vaccine every year. Healthy adults vaccinated with intramuscular inactivated vaccine have a reduced probability of influenza A or B infection and influenza-like illness, although the absolute effect may be modest.[40] [58] [59]
- Vaccination in healthy children (with live attenuated vaccine or inactivated vaccine) can reduce influenza and influenza-like illness; the effect varies across populations studied.[42]

fever with cough (common)

- Studies in older patients have shown the presence of an acute onset of fever and cough to have a positive predictive value of only 30% to 53% for influenza in non-hospitalised and hospitalised patients, respectively.[89] [90]
- A study of vaccinated older people with chronic lung disease reported that cough was not predictive of laboratory-confirmed influenza virus infection, although having both fever or feverishness and myalgia had a positive predictive value of 41%.[91]
- Young children are less likely to report typical influenza symptoms such as fever and cough.[92]
- If there is an exacerbation of fever and cough with purulent sputum and dyspnoea, a secondary bacterial pneumonia should be suspected. A chest x-ray confirms infiltrates.
- Secondary bacterial pneumonia is an important complication of influenza and contributes to approximately 25% of all influenza-associated deaths.[93]

Other diagnostic factors

sore throat (common)

- Oropharyngeal symptoms other than sore throat with associated hyperaemia are not common.

cervical lymphadenopathy (uncommon)

- A non-specific finding that may be more common in children.[88]

dyspnoea (uncommon)

- An uncommon symptom that should prompt an evaluation for a complication of influenza such as bacterial pneumonia, particularly when associated with fever, cough, and purulent sputum.[93]

**Diagnostic tests**

**1st test to order**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>clinical diagnosis</td>
<td>febrile respiratory illness during a known seasonal influenza outbreak</td>
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<td></td>
<td>There are no pathognomonic features of influenza, and further testing is indicated only when the results are likely to affect diagnosis and treatment decisions and to provide community disease surveillance.[78]</td>
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## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td><strong>viral culture</strong></td>
<td>detection of influenza virus or viral antigen</td>
</tr>
<tr>
<td>• Definitive test for laboratory diagnosis, but takes 3-10 days for results to be reported. It is not often used for initial clinical management as results may take up to 72 hours to be reported. It is used for confirming screening tests and for public health surveillance.</td>
<td></td>
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<tr>
<td>• Shell vial (centrifuge-enhanced) culture, if available, may reduce time for results to 1-3 days.</td>
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<tr>
<td>• Acceptable specimens include nasopharyngeal swab, nasal wash, bronchial wash, nasal aspirate, and sputum.</td>
<td></td>
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<tr>
<td>• Results reported in 3-10 days for results to be reported.</td>
<td></td>
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<tr>
<td><strong>direct immunofluorescent antibody staining</strong></td>
<td>detection of influenza virus</td>
</tr>
<tr>
<td>• Detects influenza A and B.</td>
<td></td>
</tr>
<tr>
<td>• Acceptable specimens include nasopharyngeal swab, nasal wash, bronchial wash, nasal aspirate, and sputum.</td>
<td></td>
</tr>
<tr>
<td>• Results reported in 2-4 hours.</td>
<td></td>
</tr>
<tr>
<td><strong>reverse transcriptase-polymerase chain reaction</strong></td>
<td>detection of influenza virus</td>
</tr>
<tr>
<td>• Detects influenza A and B.</td>
<td></td>
</tr>
<tr>
<td>• Acceptable specimens include nasopharyngeal swab, nasal wash, bronchial wash, nasal aspirate, and sputum.</td>
<td></td>
</tr>
<tr>
<td>• Results reported in 2-4 hours.</td>
<td></td>
</tr>
<tr>
<td><strong>serology</strong></td>
<td>fourfold or greater rise in antibody titre from acute to convalescent sample</td>
</tr>
<tr>
<td>• Detects influenza A and B.</td>
<td></td>
</tr>
<tr>
<td>• Assesses paired acute (collected within the first week of illness) and convalescent (collected 2-4 weeks after the acute sample) serum samples.</td>
<td></td>
</tr>
<tr>
<td>• Positive test result is indicative of recent infection.</td>
<td></td>
</tr>
<tr>
<td>• May take 2 or more weeks to receive results.</td>
<td></td>
</tr>
<tr>
<td><strong>enzyme immunoassay (EIA)</strong></td>
<td>detection of influenza virus</td>
</tr>
<tr>
<td>• Detects influenza A and B.</td>
<td></td>
</tr>
<tr>
<td>• Acceptable specimens include nasopharyngeal swab, throat swab, nasal wash, and bronchial wash.</td>
<td></td>
</tr>
<tr>
<td>• Results reported in 2 hours.</td>
<td></td>
</tr>
<tr>
<td><strong>rapid diagnostic tests</strong></td>
<td>positive for influenza A and/or influenza B, depending on particular test used</td>
</tr>
<tr>
<td>• Multiple tests are available that are designed to detect one or other, or both, of influenza A and influenza B in less than 30 minutes.</td>
<td></td>
</tr>
<tr>
<td>• Can be useful in sporadic cases of influenza that cannot be differentiated from infections caused by other respiratory viruses on clinical grounds alone.</td>
<td></td>
</tr>
<tr>
<td>• Detect low quantities of viral RNA. More sensitive than culture.</td>
<td></td>
</tr>
<tr>
<td>• Tests should be done within 24-48 hours of symptoms due to peak in viral shedding. Sensitivities and specificities of rapid diagnostic tests are approximately 70% to 75% and 90% to 95%, respectively.</td>
<td></td>
</tr>
<tr>
<td>• Relatively costly to perform.</td>
<td></td>
</tr>
<tr>
<td>• The CDC provides a list of available tests.</td>
<td></td>
</tr>
<tr>
<td><strong>chest x-ray</strong></td>
<td>normal in uncomplicated cases; may show infiltrates consistent</td>
</tr>
<tr>
<td>• Should be done to exclude either a primary viral or secondary bacterial pneumonia.</td>
<td></td>
</tr>
</tbody>
</table>
Influenza infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The radiographic appearances of community-acquired pneumonia</td>
<td>with pneumonia in</td>
</tr>
<tr>
<td>include lobar consolidation, interstitial infiltrates, and cavitations.</td>
<td>complicated cases</td>
</tr>
<tr>
<td>• It is commonly thought that lobar consolidation is suggestive of</td>
<td></td>
</tr>
<tr>
<td>bacterial pneumonia and interstitial infiltrates are suggestive of</td>
<td></td>
</tr>
<tr>
<td>pneumonia due to <em>Pneumocystis jirovecii</em> (formerly <em>P carinii</em>) and</td>
<td></td>
</tr>
<tr>
<td>viruses. However, radiologists cannot reliably differentiate bacterial</td>
<td></td>
</tr>
<tr>
<td>from non-bacterial pneumonia on the basis of the radiographic</td>
<td></td>
</tr>
<tr>
<td>appearance alone.[98]</td>
<td></td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Coronavirus disease 2019 (COVID-19)           | • Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset.  
• Signs and symptoms are similar so it may be difficult to differentiate between the conditions clinically.  
• The situation is evolving rapidly; see our COVID-19 topic for further information. | • Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for SARS-CoV-2 RNA.  
• It is not possible to differentiate COVID-19 from other causes of pneumonia on chest imaging. |
| Bacterial pneumonia                           | • In addition to cough and fever there may be pleuritic chest pain, dyspnoea, and sputum production that may be mucopurulent. | • CXR: common finding is a lobar consolidation.  
• Blood culture: positive for infecting organism.  
• Sputum culture: growth of infecting organism. |
| Respiratory syncytial virus (RSV) infection    | • Most common cause of lower respiratory tract infection in children <1 year.  
• Also a significant and often unrecognised cause of lower respiratory tract infection in both older and immunosuppressed patients.  
• Gives rise to upper and lower respiratory symptoms that peak in 3-5 days and resolve within 7-10 days.  
• Characterised by seasonal outbreaks. In the northern hemisphere, these usually occur from November to April, with a peak in January or February. In the southern hemisphere, wintertime outbreaks occur from May to September, with a peak in May, June, or July. In tropical and semi-tropical climates, the seasonal outbreaks are usually associated with the rainy season. | • Rapid assays utilising antigen capture technology that can be performed in less than 30 minutes are now available. The sensitivity and specificity of most of these tests exceed 90%, and they are a mainstay of the diagnostic algorithm in most clinical laboratories, as the identification by culture can take from 4 days to 2 weeks. |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Parainfluenza virus infection (PIV)           | • An important respiratory pathogen in adults and children; the second most common cause, after RSV, of acute lower respiratory tract infections in infants and young children.[103]  
• In adults, generally causes mild upper respiratory tract infections, but can induce life-threatening lower respiratory tract infections in immunocompromised patients.[104]  
• The seasonal patterns of PIV infection in the US have changed over the past few decades. After 1962, PIV-1 and PIV-2 began to present in epidemics, and currently appear every 2 years in the autumn. In comparison, PIV-3 occurs in annual spring epidemics, whereas seasonal patterns of PIV-4 infections have been difficult to establish, since the disease is usually mild and the virus is difficult to detect. In developing and tropical countries, parainfluenza viruses do not show seasonal variations.[105] | • Culture of PIV from the nasopharynx or lower respiratory tract remains the definitive test for diagnosis.[106]  
• Rapid antigen detection by immunofluorescence and EIA is available, with reported sensitivities of 75% to 95%.[107]  
• Serological testing can also be performed, but is time-consuming.  
• Multiplex PCR assays have become available that permit detection of a number of respiratory viruses with reported sensitivities of 95% to 100%, with excellent specificity.[108] |
Step-by-step treatment approach

The main goals of treatment at the patient level are reduction in severity and duration of symptoms and prevention of complications. At a public health level, the aim is to prevent or control outbreaks of influenza to avoid an epidemic or pandemic situation. [CDC: influenza (flu)]

When antiviral treatment is indicated, it should ideally be given within the first 48 hours of suspected or laboratory-confirmed influenza.

Treatment is recommended for people at high risk of developing complications of influenza, and therapy can be started within 48 hours of onset of symptoms. Treatment can be considered for people diagnosed with influenza 48 hours after onset of symptoms, who have continued symptoms.

All patients hospitalised for influenza require antiviral treatment.

People not at high risk of complications may be given antiviral treatment if influenza is highly suspected or confirmed, it is within 48 hours of symptom onset, and they wish to shorten the duration of their illness.

Complications may occur in any patient and it is not always possible to estimate the risk of complications, which makes treatment decisions more difficult; however, a variety of high-risk subgroups are more susceptible. At-risk groups include:[2]

- Patients with chronic pulmonary (including asthma) or cardiac conditions
- Patients with diabetes mellitus, renal disease, liver disease, chronic neurological conditions, or immunosuppression
- Patients in nursing homes or long-term care facilities
- Children aged <2 years
- Adults aged ≥65 years
- Pregnant women.

Antiviral prophylaxis after exposure to an infected individual is reserved for at-risk populations.[109] [110]

Uncomplicated influenza infection

Uncomplicated influenza infection is an acute respiratory infection caused by influenza A or B viruses that is usually self-limiting in the general population.[2] Treatment is aimed at supportive care of the symptoms associated with the respiratory tract infection. These treatments usually include antipyretics/analgesics for fever, and increased fluid intake to counter dehydration. The symptoms typically resolve in approximately 1 week; however, cough and fatigue may persist for longer.[111]

Complicated influenza infection

A more severe, complicated illness can occur in influenza infection and is associated more often with influenza A infection rather than influenza B infection.

Complications of upper respiratory tract infection include otitis media and bacterial sinusitis. Complications of lower respiratory tract infection include primary viral pneumonia and secondary bacterial pneumonia.

Treatment of these complications may require more aggressive supportive care, often necessitating hospitalisation, accompanied by antibiotics and/or antiviral treatment.
The highest rates of hospitalisation are in infants, patients aged >65 years, and patients with chronic medical conditions. Over 90% of influenza-related deaths have been in patients aged >65 years.[11]

**Antiviral treatment of early influenza infection**

The US Centers for Disease Control and Prevention (CDC) recommends antiviral treatment is given as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness, or who require hospitalisation, as well as for patients who are at higher risk for complications.[2] [109] [112] While antivirals are approved by the US Food and Drug Administration for uncomplicated acute illness, guidelines tend to recommend these drugs for complicated illness as well as for those at risk of complications. Local guidelines may vary and should be consulted.[113]

The neuraminidase inhibitors (zanamivir, oseltamivir, and peramivir) are active against both influenza A and B.[112] [114] [115] [116] [117] Oseltamivir and zanamivir have modest effectiveness against the symptoms of influenza in otherwise healthy adults,[118] and have been widely used in the treatment of 2009 influenza A/H1N1.[114] [119] [120] [121] However, there has been extensive debate over the use of oseltamivir and whether it does reduce complications in otherwise healthy adults and children.[114] [122] [123] [124] Findings from meta-analyses show that oseltamivir modestly reduces time to clinical symptom alleviation in adults with influenza, but increases the incidence of nausea and vomiting.[121] [125] The effect on mortality and complication rates was uncertain.[121] Observational studies suggest oseltamivir may reduce mortality in hospitalised patients with seasonal influenza.[126]

It has been reported that oral oseltamivir and inhaled zanamivir reduce the duration of influenza illness when started within 48 hours of symptom onset, both in children up to age 12 years and in adults.[109] [116] [127] The benefits of treatment are greatest when medicines are initiated in the first 24-30 hours of symptom onset.[128] [129]

If being prescribed, oseltamivir and zanamivir should be given to patients presenting within 2 days of onset of symptoms and given for 5 days. Peramivir is given in a single infusion, and should also be given within 2 days of symptom onset.[2] [109] [112] Peramivir may be recommended for those who are unable to take oral or inhaled neuraminidase inhibitors.

Oseltamivir is generally well tolerated in adults but may cause vomiting in children. There is less evidence for zanamivir than with oseltamivir that it reduces respiratory complications in adults.

A drug safety alert relating to oseltamivir was issued in November 2006 following reports of self-injury and delirium associated with its use. The alert states that people with influenza, particularly children, may be at an increased risk of self-injury and confusion shortly after taking oseltamivir and should be closely monitored for signs of unusual behaviour.

Pregnant women presenting with uncomplicated illness due to influenza, and who have no evidence of systemic disease, can be offered either zanamivir or oseltamivir.[109] In view of the lower systemic exposure, zanamivir is recommended as first choice, although either drug can be used. In women who are breastfeeding, oseltamivir is preferred over zanamivir. Children aged <1 year who have symptoms of seasonal influenza should be treated with oseltamivir.[109]

Baloxavir marboxil, a polymerase acidic endonuclease inhibitor, is active against both influenza A and B. The US Food and Drug Administration has approved baloxavir marboxil for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for...
no more than 48 hours, and who are otherwise healthy or at high risk of developing influenza-related complications.

The M2 inhibitors amantadine and rimantadine are only active against influenza A. There is consensus that rimantadine should not be used as first-line treatment, because cross-resistance to amantadine is high. Due to an increase in resistant isolates, physicians should seek advice from local authorities regarding antivirals based on seasonal resistance patterns.[112]

**Post-exposure antiviral chemoprophylaxis**

Should be considered for:[109][110]

- People at high risk of developing complications of influenza if illness develops shortly after influenza vaccination, before an adequate immune response develops.
- People in whom the vaccine is contraindicated. This may include anaphylaxis to egg or allergy to other components of the vaccine, febrile illness, or history of Guillain-Barre syndrome within 6 weeks of previously administered influenza vaccine.
- People who have not received the vaccine but present with acute respiratory symptoms during a known influenza outbreak.
- Unvaccinated people in close contact with those at high risk of developing complications of influenza during an influenza outbreak.
- All residents of long-term facilities or nursing homes, including those already vaccinated, if an outbreak of influenza occurs in the community where they are living.
- People who have highest risk of complications, including death. This may include immunocompromised people.
- People who were unable to receive vaccine due to shortage, if they are at high risk of developing complications of influenza.

Both oseltamivir and zanamivir have been shown to be effective as prophylaxis against infection when given early after exposure to an infected individual. One meta-analysis has shown that antivirals used prophylactically may reduce the spread of symptomatic influenza within households.[121]

**Antibiotic therapy**

Antibiotic therapy may be required for certain complications of acute influenza, such as bacterial pneumonia, sinusitis, or otitis media.

Secondary bacterial pneumonia is an important complication of seasonal influenza and contributes to 25% of all seasonal influenza deaths.[93] The most common bacteria associated with pneumonia in the context of influenza co-infection are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. Antibiotics should target these organisms.[2]
### Initial

| exposure to influenza in at-risk populations | 1st prophylactic antiviral therapy |

### Acute (summary)

#### adults

- **complicated disease or at high risk of complications:** presenting ≤48 hours after first symptoms
  - 1st antipyretic/analgesic
  - adjunct antiviral therapy
- **with bacterial superinfection of unknown source:** excluding otitis media
  - plus broad-spectrum antibiotic therapy
- **suspected or known Staphylococcus aureus superinfection:** excluding otitis media
  - plus targeted antibiotic therapy
- **with otitis media**
  - plus broad-spectrum antibiotic therapy

#### children

- **complicated disease or at high risk of complications:** presenting ≤48 hours after first symptoms
  - 1st antipyretic/analgesic
  - adjunct antiviral therapy
- **with bacterial superinfection of unknown source:** excluding otitis media
  - plus broad-spectrum antibiotic therapy
- **suspected or known Staphylococcus aureus superinfection:** excluding otitis media
  - plus targeted antibiotic therapy
- **with otitis media**
  - plus broad-spectrum antibiotic therapy
Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Influenza infection

Treatment

**Initial exposure to influenza in at-risk populations**

1st prophylactic antiviral therapy

**Primary options**

» **oseltamivir**: children <3 months of age: consult specialist for guidance on dose; children 3 months to <1 year of age: 3 mg/kg orally once daily; children ≥1 year of age and body weight ≤15 kg: 30 mg orally once daily; 15-23 kg: 45 mg orally once daily; 23-40 kg: 60 mg orally once daily; >40 kg and adults: 75 mg orally once daily

*OR*

» **zanamivir**: children ≥5 years of age and adults: 10 mg (two inhalations) once daily

» Consider post-exposure antiviral chemoprophylaxis for:

1. People at high risk of developing complications of influenza if illness develops shortly after influenza vaccination, before an adequate immune response develops; people in whom the vaccine is contraindicated (this may include anaphylaxis to egg or allergy to other components of the vaccine, febrile illness, or history of Guillain-Barre syndrome within 6 weeks of previously administered influenza vaccine); people who have not received the vaccine but present with acute respiratory symptoms during a known influenza outbreak; unvaccinated people in close contact with those at high risk of developing complications of influenza during an influenza outbreak; all residents of long-term facilities or nursing homes, including those already vaccinated, if an outbreak of influenza occurs in the community where they are living; people who have highest risk of complications, including death (this may include immunocompromised people); people who were unable to receive vaccine due to shortage, if they are at high risk of developing complications of influenza.

2. One meta-analysis has shown that antivirals used prophylactically may reduce the spread of symptomatic influenza within households.

3. Oseltamivir can be used in adults and children of all ages, and is given for 10 days (up to 6 weeks during an epidemic) for this indication. It should be started within 2 days of exposure.
<table>
<thead>
<tr>
<th>Initial</th>
</tr>
</thead>
</table>
| - Zanamivir is given for 10 days in adults and children aged >5 years for this indication, and should be started within 1.5 to 2.0 days of exposure.  
- In view of the lower systemic exposure, zanamivir is recommended as first choice in pregnant women, although either drug can be used. In women who are breastfeeding, oseltamivir is preferred over zanamivir. |
## Influenza infection: Treatment

### Acute adults

<table>
<thead>
<tr>
<th>1st antipyretic/analgesic</th>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day</td>
</tr>
<tr>
<td></td>
<td>ibuprofen: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day</td>
</tr>
</tbody>
</table>

- Antipyretics/analgesics are recommended for symptom relief of headache, fever, and myalgia.
- Ibuprofen carries a greater risk of potentially serious adverse effects compared with paracetamol.

### Complicated disease or at high risk of complications: presenting ≤48 hours after first symptoms

<table>
<thead>
<tr>
<th>Adjunct antiviral therapy</th>
<th>Treatment recommended for SOME patients in selected patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>oseltamivir: 75 mg orally twice daily</td>
</tr>
<tr>
<td></td>
<td>zanamivir: 10 mg (two inhalations) twice daily</td>
</tr>
<tr>
<td></td>
<td>peramivir: 600 mg intravenously as a single dose</td>
</tr>
<tr>
<td></td>
<td>baloxavir marboxil: body weight 40-79 kg: 40 mg orally as a single dose; body weight ≥80 kg: 80 mg orally as a single dose</td>
</tr>
</tbody>
</table>

- The US Centers for Disease Control and Prevention (CDC) recommends antiviral treatment is given as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness, or who require hospitalisation, as well as for patients who are at higher risk for complications.[109][2][112] While antivirals are approved by the US Food and Drug Administration (FDA) for uncomplicated acute illness, guidelines tend to recommend these drugs for complicated illness as well as for those...
Influenza infection

**TREATMENT**

### Acute

<table>
<thead>
<tr>
<th>with bacterial superinfection of unknown source: excluding otitis media</th>
<th>plus broad-spectrum antibiotic therapy</th>
</tr>
</thead>
</table>

- Treatment recommended for ALL patients in selected patient group

**Primary options**

- **ceftriaxone**: 2 g intravenously once daily
  
  OR

- **cefotaxime**: 1-2 g intravenously every 6-8 hours
  
  OR

- **cefuroxime**: 750-1500 mg intravenously every 6-8 hours

**Secondary options**

- The benefits of treatment are greatest when medicines are initiated in the first 24-30 hours of symptom onset.[128]

- Oseltamivir and zanamivir should be given within 2 days of onset of symptoms and given for 5 days for this indication. Peramivir is given as a single intravenous dose within 2 days of onset of symptoms.[109] Peramivir may be recommended for those who are unable to take oral or inhaled neuraminidase inhibitors.

- Baloxavir marboxil, a polymerase acidic endonuclease inhibitor, is active against both influenza A and B. The FDA has approved baloxavir marboxil for the treatment of acute uncomplicated influenza in patients aged ≥12 years who have been symptomatic for no more than 48 hours, and who are otherwise healthy or at high risk of developing influenza-related complications.

- Antivirals are not a substitute for the seasonal influenza virus vaccine.

- Pregnant women presenting with uncomplicated illness due to influenza, and who have no evidence of systemic disease, can be offered either zanamivir or oseltamivir.[109] In view of the lower systemic exposure, zanamivir is recommended as first choice, although either drug can be used.

- In women who are breastfeeding, oseltamivir is preferred over zanamivir.

- Antivirals are not a substitute for the seasonal influenza virus vaccine.
Influenza infection

**Treatment**

### Acute

- **levofloxacin**: 500 mg orally/intravenously once daily for 7-14 days; or 750 mg orally/intravenously once daily for 5 days

**OR**

- **moxifloxacin**: 400 mg orally/intravenously once daily

- Antibiotics should be reserved for certain complications of acute influenza, such as bacterial pneumonia or sinusitis.

- The choice of antibiotics should be guided by Gram stain and culture, or provide empirical antibiotics effective against the most common bacterial pathogens following influenza, namely *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Haemophilus influenzae* (some examples of suitable empiric options are listed above).[2] Treatment can be instituted as an outpatient if the patient is not in respiratory distress and is haemodynamically stable. However, close monitoring and follow-up is required to assess if the patient needs admission for inpatient care.

- When using fluoroquinolones, clinicians should be aware that they have been associated with disabling and potentially irreversible musculoskeletal and nervous system adverse events.[130][131] In addition, the US Food and Drug Administration has issued warnings about the increased risk of aortic dissection, significant hypoglycemia, and mental health adverse effects in patients taking fluoroquinolones.[132][133]

- Fluoroquinolones are not recommended in pregnancy. However, cephalosporins are suitable for use in pregnant women.

- Treatment course is generally 7-14 days.

### suspected or known Staphylococcus aureus superinfection: excluding otitis media

**plus** targeted antibiotic therapy

Treatment recommended for ALL patients in selected patient group

**Primary options**

- **oxacillin**: 2 g intravenously every 4 hours

**OR**

- **nafcillin**: 2 g intravenously every 4 hours

**TREATMENT**

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Dec 20, 2019.

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<table>
<thead>
<tr>
<th>Acute with otitis media plus broad-spectrum antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ vancomycin: 1 g intravenously every 12 hours OR</td>
</tr>
<tr>
<td>○ linezolid: 600 mg intravenously/orally every 12 hours OR</td>
</tr>
<tr>
<td>- Anti-staphylococcal coverage should be added when <em>Staphylococcus aureus</em> is a suspected source of infection. Suspicion for <em>S aureus</em> infection should be considered in patients with influenza and superimposed pneumonia on chest x-ray.</td>
</tr>
<tr>
<td>- If <em>S aureus</em> infection is confirmed, broad-spectrum antibiotic therapy should be stopped and treatment continued with either oxacillin or nafcillin.</td>
</tr>
<tr>
<td>- If MRSA is confirmed, broad-spectrum antibiotic therapy should be stopped and treatment continued with either vancomycin or linezolid.</td>
</tr>
<tr>
<td>- Treatment course is generally 10-14 days; longer courses (up to 21 days) may be required for MRSA infection.</td>
</tr>
</tbody>
</table>

Primary options

- amoxicillin: 500-875 mg orally every 12 hours for 7 days OR

Secondary options

- cefdinir: 300 mg orally every 12 hours for 10 days OR

Tertiary options

- azithromycin: 500 mg orally once daily for 3 days
Influenza infection

**Treatment**

**Acute**

<table>
<thead>
<tr>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>» clarithromycin: 250-500 mg orally every 12 hours for 7 days</td>
</tr>
<tr>
<td>Otitis media may initially be treated with amoxicillin. Lack of improvement by 48-72 hours suggests that the initial therapy was not adequate. This is usually related to infection with an organism resistant to beta-lactam antibiotics (Haemophilus influenzae and drug-resistant Streptococcus pneumoniae), thus indicating the need for a beta-lactam-sensitive drug such as amoxicillin/clavulanate or a cephalosporin.</td>
</tr>
<tr>
<td>Either azithromycin or clarithromycin may be used as an alternative in penicillin-allergic patients. However, resistant pneumococcal isolates may not respond to this therapy. [134]</td>
</tr>
<tr>
<td>Amoxicillin and cephalosporins are considered safe in pregnant women.</td>
</tr>
</tbody>
</table>

**children**

**1st antipyretic/analgesic**

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td>» paracetamol: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» ibuprofen: 5-10 mg/kg orally every 4-6 hours when required, maximum 30 mg/kg/day</td>
</tr>
<tr>
<td>Antipyretics/analgesics are recommended for symptom relief of headache, fever, and myalgia.</td>
</tr>
<tr>
<td>Ibuprofen carries a greater risk of potentially serious adverse effects compared with paracetamol.</td>
</tr>
<tr>
<td>Aspirin should not be administered to children aged &lt;16 years due to the risk of Reye syndrome.</td>
</tr>
</tbody>
</table>

**Adjunct antiviral therapy**

Treatment recommended for SOME patients in selected patient group

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td>» oseltamivir: premature infants: consult specialist for guidance on dose; children &lt;1 year of age: 3 mg/kg orally twice daily; children ≥1 year of age and body weight ≤15 kg: 30 mg orally twice daily; 15-23 kg: 45 mg</td>
</tr>
</tbody>
</table>
Influenza infection

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>or (23-40) kg: 60 mg orally twice daily; (&gt;40) kg: 75 mg orally twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>» <strong>zanamivir</strong>: children (\geq 7) years of age: 10 mg (two inhalations) twice daily</td>
</tr>
<tr>
<td></td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>» <strong>peramivir</strong>: children (\geq 2) years of age: 12 mg/kg intravenously as a single dose, maximum 600 mg/dose</td>
</tr>
<tr>
<td></td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>» <strong>baloxavir marboxil</strong>: children (\geq 12) years of age and body weight 40-79 kg: 40 mg orally as a single dose; children (\geq 12) years of age and body weight (\geq 80) kg: 80 mg orally as a single dose</td>
</tr>
</tbody>
</table>

» The US Centers for Disease Control and Prevention (CDC) recommends antiviral treatment is given as soon as possible for children with confirmed or suspected influenza who have severe, complicated, or progressive illness, or who require hospitalisation, as well as for children who are at higher risk for complications.[2] [109] [112] While antivirals are approved by the US Food and Drug Administration (FDA) for uncomplicated acute illness, guidelines tend to recommend these drugs for complicated illness as well as for those at risk of complications. Local guidelines may vary and should be consulted.[113]

» The benefits of treatment are greatest when medicines are initiated in the first 24-30 hours after symptom onset.[135] [128] [136] [129]

» Oseltamivir and zanamivir should be given within 2 days of onset of symptoms and given for 5 days for this indication. Peramivir may be given to children aged 2 years and older who have been symptomatic for no more than 2 days.[109] [112] Peramivir may be recommended for those who are unable to take oral or inhaled neuraminidase inhibitors.

» Baloxavir marboxil, a polymerase acidic endonuclease inhibitor, is active against both influenza A and B. The FDA has approved baloxavir marboxil for the treatment of acute uncomplicated influenza in children aged \(\geq 12\) years who have been symptomatic for no more than 48 hours, and who are otherwise healthy.
**Acute**

<table>
<thead>
<tr>
<th>with bacterial superinfection of unknown source: excluding otitis media</th>
<th>plus</th>
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<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
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<tr>
<td><strong>Primary options</strong></td>
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<tr>
<td>» ceftriaxone: 50-75 mg/kg/day intravenously</td>
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<tr>
<td>» Antibiotics should be reserved for certain complications of acute influenza, such as bacterial pneumonia or sinusitis.</td>
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<tr>
<td>» The choice of antibiotics should be guided by Gram stain and culture, or provide empirical antibiotics effective against the most common bacterial pathogens following influenza, namely <em>Streptococcus pneumoniae</em>, <em>Staphylococcus aureus</em>, or <em>Haemophilus influenzae</em> (an example of suitable empiric option is listed above).[2] Treatment can be instituted as an outpatient if the patient is not in respiratory distress and is haemodynamically stable. However, close monitoring and follow-up is required to assess if the patient needs admission for inpatient care.</td>
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<tr>
<td>» Treatment course is generally 7-14 days.</td>
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<table>
<thead>
<tr>
<th>suspected or known <em>Staphylococcus aureus</em> superinfection: excluding otitis media</th>
<th>plus</th>
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<tbody>
<tr>
<td><strong>Targeted antibiotic therapy</strong></td>
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<tr>
<td><strong>Primary options</strong></td>
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<tr>
<td>» oxacillin: 100-200 mg/kg/day intravenously given in divided doses every 6 hours, maximum 12 g/day</td>
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<tr>
<td>OR</td>
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<tr>
<td>» nafcillin: 50-200 mg/kg/day intravenously given in divided doses every 4-6 hours, maximum 12 g/day</td>
<td></td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» vancomycin: 10-15 mg/kg intravenously every 6 hours, maximum 2000 mg/day</td>
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</tbody>
</table>
Acute

with otitis media plus broad-spectrum antibiotic therapy

Treatment recommended for ALL patients in selected patient group

Primary options

- amoxicillin: 80-90 mg/kg/day orally given in divided doses every 12 hours for 10 days

OR

- amoxicillin/clavulanate: >3 months of age: 80-90 mg/kg/day orally given in divided doses every 12 hours for 10 days
  Dose refers to amoxicillin component.

Secondary options

- cefdinir: >6 months of age: 14 mg/kg/day orally for 10 days

OR

- cefuroxime: 30 mg/kg/day orally given in divided doses every 12 hours for 10 days

Tertiary options

- azithromycin: >6 months of age: 10 mg/kg/day orally on the first day, followed by 5 mg/kg/day for 4 days; or 10 mg/kg/day orally for 3 days; or 30 mg/kg/day orally as a single dose
Influenza infection

Treatment

Acute

OR

- clarithromycin: >6 months of age: 15 mg/kg/day orally given in divided doses every 12 hours for 10 days

- More than 80% of children with pneumococcal acute otitis media will respond to high-dose amoxicillin treatment.[137]

- Lack of improvement by 48-72 hours in a patient treated with antimicrobial therapy suggests that the initial therapy was not adequate. This is usually related to infection with an organism resistant to beta-lactam antibiotics (Haemophilus influenzae and drug-resistant Streptococcus pneumoniae), thus indicating the need for a beta-lactam-sensitive drug such as amoxicillin/clavulanate or a cephalosporin.

- Either azithromycin or clarithromycin may be used as an alternative in penicillin-allergic patients. However, resistant pneumococcal isolates may not respond to this therapy.[134]
Emerging

Intravenous zanamivir

The European Medicines Agency has approved an intravenous formulation of zanamivir for the treatment of complicated and potentially life-threatening influenza in children ≥6 months of age and adults. The indication is for patients in whom other treatments for influenza, including the inhaled formulation of zanamivir, are unsuitable, and/or the patient’s influenza virus is known or suspected to be resistant to other treatments. In the US, the intravenous formulation is only available through a compassionate use program or enrolment in a clinical trial.

Needle-free technology

Needle-free jet injection for administration of influenza vaccine might avoid the issue of needle phobia and the risk of needle-stick injury.[138]

Combination antiviral therapy

Combining two antivirals that act on different aspects of the viral lifecycle may offer benefits over single agents alone, although options are limited by the small number of antivirals available.[139] Studies in mice demonstrate therapeutic synergism when oseltamivir is combined with amantadine,[140] or with favipiravir.[141] An in vitro study suggests that amantadine and oseltamivir combination therapy may reduce the emergence of drug-resistant influenza A virus.[142] However, caution may be warranted, as a study of combined oseltamivir-zanamivir found it to be less effective than oseltamivir alone.[143]

Recombinant sialidase fusion protein DAS181

Currently under development, this agent targets host respiratory cells rather than the influenza virus itself, specifically the sialic acid receptor used by the influenza virus to attach to the airway epithelium.[139] DAS181 is a sialidase fusion protein consisting of the sialidase catalytic domain of Actinomyces viscosus, fused with a cell surface anchoring sequence. The inhaled fusion protein removes the receptors for influenza attachment on the respiratory epithelium. Studies to date have shown in vitro effectiveness against both influenza A and B,[144] and in vitro and in vivo effectiveness against human parainfluenza viruses.[145]

Cyanovirin-N

Cyanovirin-N is a protein that interacts with the haemagglutinin cell surface protein of both influenza A and influenza B viruses in vitro.[135] It confers antiviral properties by blocking viral entry,[139] but further development has been hindered by problems relating to immunogenicity and cytotoxicity. An initial study with a novel PEGylated cyanovirin-N derivative has; however, yielded positive results.[146]

Short-interfering RNAs

Although currently only studied in mice, short-interfering RNAs specific for conserved regions of the influenza gene reduced viral replication when administered intravenously. More recently, RNA interference has been shown to inhibit influenza virus infection in co-operation with interferon gamma.[147]

Favipiravir

A substituted pyrazine that inhibits virus RNA polymerase.[139] In vitro and in vivo studies have shown inhibition of viral replication and activity against viruses that are resistant to both amantadines and neuraminidase inhibitors. Favipiravir blocks the replication of many strains of influenza virus, including the H7N9 avian virus.[148] In addition, it is active against many arena-, bunya-, flavi-, alpha-, picorna-, and noroviruses.
**Viramidine**

A prodrug of ribavirin, viramidine targets the cellular enzyme IMP dehydrogenase, which is involved in viral RNA synthesis.[139] It is active against seasonal and H5N1 influenza A viruses,[149] and can be administered intravenously, orally, or by aerosol.

**DNA vaccine**

A trivalent DNA vaccine has been developed with three plasmids expressing haemagglutinin from different seasonal influenza virus strains. It demonstrated protection against influenza and had a good safety profile.[150] In a phase I clinical trial, adjuvanted-monovalent H5 DNA vaccines were well tolerated and induced haemagglutination inhibition response rates similar to that of inactivated protein-based H5 vaccines.[151] The results suggest that adjuvanted DNA vaccines with rapid vaccine production could be useful for pandemic control.

**VIS410**

VIS410 is a monoclonal antibody that has been designed to target all known strains of influenza A. It is directed against a specific epitope on haemagglutinin, a surface protein used for cell binding and entry, and is designed to terminate the influenza virus replication cycle. It is is being developed to treat hospitalised patients with influenza A and is currently in phase 2 trials.
Recommendations

Monitoring

The CDC and the WHO track and report seasonal influenza virus isolates across the world to monitor disease activity and predict the appropriate components for the annual seasonal influenza vaccine. This information may help physicians to track any outbreaks, epidemics, or pandemics to prepare their community better. This information is updated weekly during influenza season. [CDC: FluView: weekly influenza surveillance report]

Patient instructions

Advise patients with influenza to avoid close contact with uninfected individuals so as to prevent transmission of respiratory secretions and therefore limit spread of the virus in the community.

Make patients aware that the seasonal influenza vaccine is an annual vaccine whose components are reflective of the predicted strains for that season. Thus it needs to be administered each season.

Patients should also be aware of fraudulent and unapproved over-the-counter products that claim to prevent or cure influenza. The US Food and Drug Administration has warned consumers that while there are legal over-the-counter products available to reduce influenza symptoms, there are no legally marketed over-the-counter drugs available for prevention or cure of influenza.[164]
## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bacterial pneumonia</strong></td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Most commonly occurs in high-risk populations, such as those with chronic medical conditions, and is associated with 25% of all influenza deaths.[93] An estimated 11.5% of lower respiratory tract infections (LRTI) are caused by seasonal influenza. Adults aged over 70 years are particularly susceptible to influenza LRTIs.[153] The most common organisms involved are <em>Streptococcus pneumoniae</em>, <em>Staphylococcus aureus</em>, and <em>Haemophilus influenzae</em>. [154] Treat with antibiotics that provide coverage against these bacterial organisms or as indicated by culture results. Chest x-ray will reveal typical infiltrates.</td>
<td></td>
<td></td>
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<tr>
<td><strong>viral pneumonia</strong></td>
<td>short term</td>
<td>low</td>
</tr>
<tr>
<td>Primary influenza pneumonia occurs when influenza virus infection directly involves the lung tissue. An estimated 11.5% of lower respiratory tract infections (LRTI) are caused by seasonal influenza. Adults aged over 70 years are particularly susceptible to influenza LRTIs, which caused an estimated 9,459,000 hospitalisations and 145,000 deaths globally in 2017.[153] Suspicion should be raised when symptoms persist and increase instead of resolving in a patient with acute influenza. High fever, dyspnoea, and even progression to cyanosis can be seen.[4] Most commonly occurs in high-risk populations, such as those with chronic medical conditions.</td>
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<tr>
<td><strong>otitis media</strong></td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Complicates the course of influenza in 10% to 50% of children.[155] Treatment with oseltamivir reduces the incidence of new acute otitis media infections in children.[156] Aetiology is a bacterial superinfection most commonly associated with <em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, or <em>Moraxella catarrhalis</em>. [157] Treatment is based on coverage for these organisms.</td>
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<tr>
<td><strong>rhabdomyolysis/myositis</strong></td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Reported more frequently in children, myositis typically presents as sore muscles of the legs. The pathogenesis is not well understood; however, the presence of influenza virus in affected muscles has been noted.[158] Characterised by increased levels of creatine phosphokinase in serum and, possibly, myoglobinuria with renal failure.[159] [160]</td>
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<tr>
<td><strong>encephalitis</strong></td>
<td>short term</td>
<td>low</td>
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### Complications

<table>
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<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>A retrospective cohort study of 842 children in the US with laboratory-confirmed influenza in the years between 2000 and 2004 found the incidence of neurological complications was 4 cases per 100,000 person-years.[155] Neurological complications were more frequent for ages 6 months to 4 years and in those with underlying neurological or neuromuscular disease. Encephalitis occurs when the virus enters the CNS. Since abnormalities in brain function are common in encephalitis, monitor for altered mental status, motor or sensory deficits, altered behaviour and personality changes, and speech or movement disorders. Treatment is supportive.</td>
<td>short term</td>
<td>low</td>
</tr>
<tr>
<td>transverse myelitis</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>This is a segmental spinal cord injury caused by acute inflammation. Typically the inflammation is bilateral, producing weakness and sensory disturbance below the level of the lesion. MRI of the spinal cord shows gadolinium-enhancing signal abnormality in the affected segment(s). Patients are often treated with parenteral corticosteroids.[161]</td>
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<tr>
<td>aseptic meningitis</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Patients with meningitis may be uncomfortable, lethargic, and/or distracted by headache, but their cerebral function remains normal. Treatment is supportive.</td>
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<tr>
<td>Guillain-Barre syndrome (GBS)</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>A heterogeneous condition with several variant forms. Most often, GBS presents as an acute paralysing illness provoked by a preceding infection. The cardinal clinical features of GBS are progressive, fairly symmetrical muscle weakness accompanied by absent or depressed deep tendon reflexes. Treatment is mostly supportive, although disease-modifying agents such as corticosteroids and immunoglobulin infusions have been used.[162]</td>
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<tr>
<td>toxic shock syndrome</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Toxic shock syndrome, associated with <em>Staphylococcus aureus</em> infection and acute <em>Staphylococcus aureus</em> infection, has been described after both influenza A and B infections in case reports.[163]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-influenza encephalopathy</td>
<td>long term</td>
<td>low</td>
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Toxic shock syndrome, associated with *Staphylococcus aureus* infection and acute *Staphylococcus aureus* infection, has been described after both influenza A and B infections in case reports.[163]
Influenza infection

Complications | Timeframe | Likelihood
---|---|---
A retrospective cohort study of 842 children in the US with laboratory-confirmed influenza in the years between 2000 and 2004 found the incidence of neurological complications was 4 cases in 100,000 person-years.[155]

Neurological complications were more frequent for ages 6 months to 4 years and in those with underlying neurological or neuromuscular disease.

Monitor for altered mental status, motor or sensory deficits, altered behaviour and personality changes, and speech or movement disorders.

Prognosis

**Uncomplicated seasonal influenza infection**

Seasonal influenza is usually a self-limiting acute respiratory illness that recurs each winter season as different strains emerge. Annual influenza vaccines are available to immunise against the 3 expected strains to pass through a community.[152] If seasonal influenza is contracted, institution of antivirals within 36 to 48 hours of onset of symptoms will decrease days of illness by 1 to 2 days and reduce lower respiratory tract complications.[109] [116]

**Complicated seasonal influenza: viral pneumonia**

Patients considered at high risk for seasonal influenza may develop a lower respiratory tract complication of viral pneumonia. This may require more aggressive supportive care or hospitalisation.

**Complicated seasonal influenza: bacterial pneumonia**

Patients who have an initial improvement of their respiratory illness followed by recurrence of fever and cough with productive sputum may have a bacterial pneumonia complicating the seasonal influenza infection. This may require more aggressive supportive care, appropriate antibiotic therapy, and/or hospitalisation.
## Diagnostic guidelines

### North America

**Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza**

*Published by:* Infectious Diseases Society of America  
*Last published:* 2018

**Influenza signs and symptoms and the role of laboratory diagnostics**

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2016

## Treatment guidelines

### Europe

**PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza**

*Published by:* Public Health England  
*Last published:* 2019

**Influenza: the Green Book: chapter 19**

*Published by:* Public Health England  
*Last published:* 2019

**Immunisation guidelines for Ireland: chapter 11 influenza**

*Published by:* Health Service Executive, Ireland  
*Last published:* 2019

**Flu vaccination: increasing uptake**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2018

**Amantadine, oseltamivir and zanamivir for the treatment of influenza**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2009

**Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2008

### International

**Recommended composition of influenza virus vaccines for use in the 2019-2020 northern hemisphere influenza season**

*Published by:* World Health Organization  
*Last published:* 2018
<table>
<thead>
<tr>
<th>Topic</th>
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<th>Last published</th>
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<tbody>
<tr>
<td>Recommended adult immunization schedule for ages 19 years or older, United States, 2019</td>
<td>Centers for Disease Control and Prevention</td>
<td>2019</td>
</tr>
<tr>
<td>Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2019</td>
<td>Centers for Disease Control and Prevention</td>
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</tr>
<tr>
<td>Influenza antiviral medications: summary for clinicians</td>
<td>Centers for Disease Control and Prevention</td>
<td>2018</td>
</tr>
<tr>
<td>Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2019-20 influenza season</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>Recommendations for obstetric health care providers related to use of antiviral medications in the treatment and prevention of influenza</td>
<td>Centers for Disease Control and Prevention</td>
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</tr>
<tr>
<td>Guidance for the prevention and control of influenza in the peri- and postpartum settings</td>
<td>Centers for Disease Control and Prevention</td>
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<td>Prevention strategies for seasonal influenza in healthcare settings</td>
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<td>A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases</td>
<td>Infectious Diseases Society of America; American Society for Microbiology</td>
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<td>Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza</td>
<td>Infectious Diseases Society of America</td>
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### North America

**Antiviral agents for the treatment and chemoprophylaxis of influenza**

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2011

### Africa

**Influenza guideline for South Africa: update 2008**

*Published by:* South African Thoracic Society  
*Last published:* 2008

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Online resources

1. CDC: FluView - weekly influenza surveillance report (external link)

2. CDC: influenza (flu) (external link)

3. WHO: influenza update (external link)

4. CDC: influenza symptoms and the role of laboratory diagnostics (external link)
Key articles

- Centers for Disease Control and Prevention. Influenza (flu). November 2019 [internet publication].  Full text


References


<table>
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Influenza infection


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132. US Food and Drug Administration. FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. July 2018 [internet publication]. Full text

133. US Food and Drug Administration. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. December 2018 [internet publication]. Full text


164. US Food & Drug Administration. FDA warns of fraudulent and unapproved flu products. March 2018 [internet publication].  Full text
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