Influenza – prevention is better than cure

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Influenza, caused by influenza A or influenza B viruses, is usually a self-limiting disease in healthy patients but is associated with increased morbidity and mortality in high-risk groups and can result in more than 11 000 deaths annually in South Africa. Non-pharmacological prevention measures reduce the spread of infection, and the incidence of influenza was reduced following the implementation of these measures in 2020 to prevent the spread of coronavirus infections. Influenza vaccination is currently the most effective method to prevent and control influenza infection. It is, on average, around 59% effective depending on the patient's age, comorbidities and accuracy of the strains predicted for the season. Treatment for mild influenza focuses on the management of symptoms. Patients at high risk for severe and/or complicated disease should be treated for five days with antivirals (oseltamivir or zanamivir), preferably within 48 hours of onset of symptoms.

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Introduction

In otherwise healthy individuals, influenza is an acute, unpleasant, but usually self-limiting disease caused by influenza A or influenza B viruses and usually resolves within two to seven days.[1] However, it is associated with increased morbidity and mortality in high-risk groups.[2] Three influenza pandemics occurred in the last century (1918, 1957 and 1968), and the first pandemic of this century caused by an influenza A (H1N1) virus was declared by the World Health Organization (WHO) in June 2009.[1]

A modelling study from South Africa estimated that around 10 737 847 (19.8%) of the population was affected annually by influenza-associated illness between 2013 and 2015. The majority of these were mild episodes, 128 173 cases were severe-illness episodes, and 11 536 cases were fatal.[3] Influenza-related deaths were higher among infants younger than one year and individuals older than 65.[3] For patients older than five years, an estimated 30% of influenza-associated deaths were in HIV-infected patients, and mortality rates in pregnant women are three times higher compared to non-pregnant women.[3]

Transmission

Influenza is spread from person to person through inhalation of droplets or aerosols (expelled through sneezing, coughing or talking) or by touching mucous membranes following contact with contaminated objects.[1,3-6] The incubation period is between 1 and 4 days (2 days on average). Patients are infectious one day before onset of symptoms, most infectious 3–4 days after onset of symptoms, and 5–7 days after onset of symptoms.[3,4] Young children, older patients, patients with chronic medical conditions, obese patients, and immunocompromised patients can shed the virus for more extended periods (weeks to months).[3,6]

Prevention

Non-pharmacological

It is important to prevent influenza, especially in patients at risk of severe or complicated influenza. Patients with influenza can reduce the spread by staying at home until at least 24 hours after the fever has resolved.[3] Patients should avoid close contact, such as kissing and sharing drinks with others, especially those who are at high risk of severe disease.[3] Patients should sneeze and cough into a tissue or the sleeve and wash hands regularly with soap and water, or disinfect with an alcohol-based hand rub or spray.[3] Surfaces that are regularly touched or shared, such as doorknobs or remote controls, should be wiped regularly with a disinfectant.[3]

In residential homes, isolation for five days from the onset of symptoms or quarantining sick patients together may help contain infections. It may be necessary to close residential homes until the infection is under control. Closing schools (full or partial) is not generally recommended but may be considered for logistical purposes.[3]

Despite continued testing and surveillance, very few cases of influenza were detected in 2020 and 2021, most likely due to the non-pharmaceutical measures implemented to control

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.[3]

The role of antivirals

Antiviral chemoprophylaxis is not currently recommended. However, the WHO guidelines state that patients at high risk of severe disease who have been exposed to influenza, may benefit from presumptive antiviral treatment, or could alternatively be monitored closely to start antiviral treatment as soon as possible after the onset of symptoms.[3]

Vaccination

Two inactivated quadrivalent influenza vaccines are currently available in South Africa. Both can be administered either intramuscularly or via deep subcutaneous route (which is preferable for patients with bleeding conditions).

- Vaxigrip Tetra is registered as a 0.5 ml dose for patients 6 months and older.[7]
- Influvac Tetra is also given as a 0.5 ml dose but is registered for use only from 3 years of age.[8]

For children 6 months through 8 years of age, a second dose of the flu vaccine is recommended, if it is the first time ever that the child is receiving a flu vaccine.[3] In subsequent seasons, only one dose will be required.[3]

Influenza vaccines are indicated for active immunisation throughout pregnancy and also provide passive protection of infants from birth to ~6 months of age following vaccination of pregnant women.[7] Patients with a mild allergic reaction to egg (hives only), may receive the flu vaccine whilst patients who had an anaphylactic reaction to egg may have the vaccine administered in a facility under the supervision of a health care provider who can recognise and manage severe allergic reactions.[9]

Protective antibody responses take about two weeks to develop. Therefore, the vaccine should be given as soon as it becomes available in the new influenza season (usually around March in the southern hemisphere), to provide protection before the influenza season starts. Since the incubation period for influenza is less than four days, and protection only occurs two weeks after vaccination, the vaccine is not effective as post-exposure prophylaxis.[3]

Between 2005 and 2015, estimated vaccine efficacy varied between 46% and 87% when there was a good match with circulating strains and between 14% and 38% when there was a mismatch. Overall efficacy was estimated to be around 59% in healthy adults. The vaccine may be less effective in certain groups such as immunocompromised individuals, infants, and the elderly. However, vaccination may reduce the incidence of severe disease and mortality and is recommended for these patients.[3]

Vaccination is also recommended for all healthcare workers, all patients at high risk of severe and/or complicated disease, anyone in contact with high-risk patients, and anyone wishing to minimise their risk of contracting influenza.[3]

Signs and symptoms of influenza

Adult patients usually present with an abrupt onset of fever (ranging between 37.8 °C and up to 41.1 °C), myalgia and a non-productive cough.[4] Other symptoms may include malaise, sore throat, nausea, nasal congestion, rhinitis, arthralgia, and headache.[3,4]

Children are more likely to present with higher fevers, febrile seizures, and gastrointestinal symptoms such as nausea, vomiting, poor appetite, and diarrhoea.[3,5]

Older patients (≥ 65 years of age) and immunosuppressed patients are more likely to have subtle signs and symptoms. In older patients, typical symptoms such as sore throat, myalgias and fever may be absent, while symptoms such as altered mental status, weakness, dizziness, anorexia, and malaise are often more prominent.[4]

Symptoms may also vary between different types and subtypes of influenza. For instance, influenza B is more typically associated with musculoskeletal findings than influenza A. Gastrointestinal symptoms were more commonly reported with the 2009 H1N1 influenza pandemic when compared to other seasonal influenza strains.[1]

Symptoms usually start improving after three days, with full recovery within 10 to 14 days (longer in patients ≥ 65 years). Symptoms like cough may persist, especially in younger children and weakness and fatigue may last for several weeks in older children and adults.[4,5]

Risk factors for severe or complicated influenza

Certain groups of people are at greater risk of developing severe or complicated influenza. They include:[3]

- Young children (particularly those younger than two years of age)
- Patients ≥ 65 years of age
- Patients ≤ 18 years on chronic aspirin therapy
- Pregnant women (including up to 2 weeks post-partum)
- HIV-infected patients
- Patients with tuberculosis
- Morbidly obese patients (body mass index ≥ 40)
- Patients with other chronic medical conditions
  - Immunosuppression, e.g. due to medication use or malignancies
  - Pulmonary diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis
  - Cardiovascular diseases such as congenital heart disease, congestive heart failure, coronary artery disease (excluding hypertension)
  - Metabolic diseases such as diabetes

- Renal disease
- Hepatic disease
- Haemoglobinopathies such as sickle cell disease
- Neurologic and neurodevelopmental diseases such as disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, seizure disorders, stroke, mental retardation, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury

Complications

Patients with complicated influenza may present with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, tachypnoea, lower chest wall indrawing and inability to feed), central nervous system (CNS) involvement and/or a significant exacerbation of an underlying medical condition, including COPD, asthma, coronary artery disease or heart failure.[3,4]

Pneumonia is the most common complication of influenza. It can include secondary bacterial pneumonia (often with *S. pneumoniae*, *S. aureus* or *S. pyogenes*), mixed bacterial and viral pneumonia or primary influenza pneumonia. Primary influenza pneumonia should be suspected if patients have persistent symptoms including fever and dyspnoea. Patients with secondary bacterial pneumonia often demonstrate initial improvement of influenza symptoms, including fever, followed by a relapse of fever with a cough productive of purulent sputum. Mixed viral and bacterial pneumonia may present as either gradual progressive disease or transient improvement followed by worsening.[4]

Cardiovascular complications may include myocardial infarction, heart failure, myositis, myocarditis, and pericarditis, whilst CNS complications may include seizures, encephalopathy, encephalitis, cerebrovascular accident, acute disseminated encephalomyelitis, and Guillain-Barré syndrome. Musculoskeletal complications such as myositis and rhabdomyolysis occur more frequently in children than in adults. Other complications may include parotitis, bronchitis, sinusitis, and reactive airway disease.[3,4]

Treatment

Patients should take in sufficient amounts of fluids to prevent dehydration. Consumption of warm liquids may help thin secretions, soothe the mucosa, and increase the flow of nasal mucus, making it easier to remove.[10]

Paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) are indicated as analgesics and to manage fever.[11,12] Paracetamol remains the first choice of treatment for sore throat, headache, myalgia, and fever in pregnancy.[11] Aspirin and ibuprofen have been associated with adverse pregnancy and infant outcomes. Aspirin is not recommended for children due to the risk of Reye's syndrome.[12]

Symptomatic treatment of cough and rhinorrhoea with over-the-counter (OTC) combination products is not recommended in children as they have no proven benefit and have been associated with fatal overdose in children.[12] Normal saline nose drops may be used to remove mucus from nasal passages and reduce nasal congestion, whilst saline irrigations (using sterile or bottled water) may also be used in older children.[10]

For children older than 12 years and adults, antihistamine and decongestant combination products may be more beneficial than either component alone to relieve symptoms of nasal congestion and rhinorrhoea.[13] Nasal sprays containing cromolyn or ipratropium are options for treating nasal symptoms in pregnancy.[11]

Antibiotics are not effective for the treatment of influenza but may be indicated for the treatment of bacterial complications such as bacterial pneumonia, otitis media or sinusitis.[3,11]

Antiviral treatment is only recommended for patients with complicated or severe illness (including all hospitalised patients) and for patients at higher risk of influenza complications.[3] Treatment should be started as soon as possible (preferably within 48 hours of symptom onset). Antiviral treatment is not recommended for patients who do not fall into high-risk groups or present with uncomplicated influenza.[3] In hospitalised patients with severe, complicated, or progressive disease, antiviral treatment may still be beneficial even when started more than 48 hours after onset of symptoms.[3]

Neuraminidase inhibitors available for the treatment of influenza in South Africa include oseltamivir (Tamiflu) and zanamivir (Relenza). Adults should be treated with 75 mg oseltamivir twice daily for 5 days, while dosing for children depends on the age and weight of the child (Table I).

Table I: Recommended dosage and duration of oseltamivir treatment for influenza in children[3]

Age	Dose
Premature neonates born at < 38 weeks gestation	1 mg/kg twice daily for 5 days
Neonates born at 38–40 weeks (full-term)	1.5 mg/kg twice daily for 5 days
Infants aged between 1 day and 12 months	3 mg/kg twice daily for 5 days
Infants and children ≥ 1 year • ≤ 15 kg • > 15–23 kg • > 23–40 kg • > 40 kg	 • 30 mg twice daily for 5 days • 45 mg twice daily for 5 days • 60 mg twice daily for 5 days • 75 mg twice daily for 5 days

The dose for treatment with zanamivir in adults and children older than 7 years is 10 mg (2 x 5 mg inhalations) twice daily for 5 days.[3]

Conclusion

Most influenza infections are mild, and symptoms can be managed effectively at home.[3] However, influenza can cause severe illness in certain high-risk patients and can result in complications (that may require hospitalisation), or even death.[1] Symptomatic treatment may relieve symptoms, but patients at high risk should receive antiviral treatment, preferably within 48 hours after onset of symptoms.[3] Vaccination is the most effective method available for the prevention and control of influenza infection and is recommended for all healthcare workers, patients in high-risk groups and any person who wants to reduce the risk of contracting influenza.[3]

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