Influenza 2025: WHO Guidelines for South Africa's season

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Introduction

This is a summary of the clinical practice guidelines for influenza that was published by the World Health Organization and is referenced in full at the end of this article.

The updated 2024 guidelines provide recommendations on the management of both severe and non-severe influenza, including recommendations on the use of antiviral medications to prevent influenza virus infection in individuals exposed to the virus within the previous 48 hours. This update applies to patients with seasonal influenza viruses, pandemic influenza viruses, and novel influenza A viruses known to cause severe illness in infected humans.

This update also includes baseline risk estimates for hospitalisation and death, as well as proposed definitions of patients at high or extremely high risk of developing severe influenza, to enable the recommendations to be targeted appropriately.

Influenza is an acute respiratory infection caused by the influenza virus.

There are two types of influenza viruses:

1. **Seasonal and pandemic influenza** are caused by influenza A, B, and C viruses. Influenza viruses are single-stranded RNA viruses. Influenza A is further subdivided into subtypes based on their main antigenic determinants, the haemagglutinin (H or HA) and neuraminidase (N or NA) transmembrane glycoproteins. The B type is in lineages, currently circulating either B/Yamagata or B/Victoria. The influenza C virus is not captured by surveillance and thus not of importance. Influenza D is found in cattle and never in humans.

Only influenza A and B viruses cause epidemics in humans. Influenza A viruses are further subdivided into 18 H (H1–H18) and 11 N (N1–N11) subtypes, but only three haemagglutinin subtypes, H1, H2, and H3, and two neuraminidase subtypes, N1 and N2, have circulated consistently in the human population and are responsible for annual epidemics.

Only Influenza A causes pandemics. The A(H1N1) is also classified as A(H1N1)pdm09, as it caused the pandemic in 2009 and replaced the previous A(H1N1) virus, which had circulated prior to 2009. The A(H3N2) virus caused the 1968 pandemic and has continued to circulate as a seasonal influenza A virus, with the influenza B viruses currently circulating either the B/Yamagata or B/Victoria lineages.

2. **Zoonotic Influenza**: Humans can sporadically be infected with novel Influenza A viruses of animal origin, such as avian influenza A virus subtypes A(H5N1), A(H5N6), A(H7N9), A(H7N7) and A(H9N2) and swine influenza A virus subtypes A(H1N1), A(H1N2) and A(H3N2).

Antigenic drift occurs when the influenza virus undergoes small changes, often allowing us to retain some level of immunity. In contrast, antigenic shift involves a major change in the virus, resulting in a completely new strain - also known as a novel virus - to which the population has little or no immunity. This can lead to widespread outbreaks or even pandemics, often causing more severe illness, increased hospitalisations, and higher death rates.

The South African influenza season ranges from May to September.

Worldwide, the influenza season causes approximately 3 billion cases, of which 3–5 million are severe cases, resulting in 290 000 - 650 000 deaths.

In 2018, there were 109.5 million cases of influenza, 870 000 admissions, and 34 800 deaths due to influenza in children under the age of 5 years.

In South Africa during the 2013–2015 seasons, 10.7 million people had influenza, of which 98.7% were mild, 1.2% were severe, and 0.1% were fatal. The highest rate of admissions to hospitals was in the age groups less than 5 years and older than 65 years, and in people living with HIV (PLWH). In the severe and fatal category, most were younger than 1 year and older than 65 years. In the age group older than 5 years, 30% of deaths were due to PLWH. Pregnant women are also at high risk, especially if HIV positive.

The highest number of mild cases was between the ages of 5 and 24 years.

Viruses are transmitted either by **airborne transmission** when the virus is deposited into the air and inhaled by another person or by **direct deposition** when virus particles are deposited on the facial surface, nose, mouth, and conjunctiva and so enter the respiratory tract. It can also be spread by **direct contact** via the hands from certain surfaces, such as counters and doorknobs. The incubation period is 1–4 days, and viruses are shed a few days before and 5–7 days after onset. This can be longer in severely hospitalised persons.

Diagnosis of influenza

Signs and symptoms of influenza vary from person to person and are very non-specific, making the diagnosis difficult and often based solely on clinical grounds.

PCR testing remains the gold standard for diagnosing influenza; however, its turnaround time is often too slow to guide timely clinical decisions. Rapid tests, such as Nucleic Acid Amplification Tests (NAATs), offer results within 30 minutes, making them more useful in acute care settings. However, their accuracy is highly sample-dependent - factors such as the timing of sample collection during the illness, the site of collection, and how the sample is transported and processed can all affect the results. It is recommended that samples be collected from both the nose and throat in patients who are not in respiratory failure. The nasopharyngeal swab - familiar to many from the COVID-19 pandemic - remains the preferred method for sample collection. It's important to consult with your laboratory regarding the appropriate swab type, transport medium, and correct procedures for sample transport. For severely ill patients, if upper respiratory tract samples test negative, samples should be collected from the lower respiratory tract. This can include sputum, endotracheal aspirates, or bronchoalveolar lavage specimens.

Management of Influenza

Non-severe or uncomplicated influenza presents with the sudden onset of cough, rhinitis, sore throat, headache, myalgia and arthralgia with or without fever. This normally resolves within 3–7 days, but the cough can persist for up to 14 days without requiring medical attention and can be managed with symptomatic treatment.

Severe or complicated influenza refers to patients who require hospital admission due to conditions such as pneumonia, sepsis, septic shock, acute respiratory distress syndrome (ARDS), multiorgan failure, or worsening of existing chronic medical conditions. Additionally, novel influenza strains with known high mortality rates – or those with unknown mortality – are also classified as severe, even if they do not meet the criteria listed above.

Table I: Classification of high-risk groups

Age	≥ 65 years
Chronic respiratory disease	Asthma Tuberculosis COPD
Cardiovascular disease	Congestive cardiac failure Ischaemic heart disease Congenital heart disease
Neurological disease	Stroke Mental retardation, developmental delay Cerebral palsy Spinal cord injury Peripheral nerve disease Epilepsy
Renal disease	
Metabolic disease	Diabetes
Immunocompromised patients	Malignancy HIV Patients receiving chemotherapy
Pregnancy	Up to 6 weeks postpartum
Novel Influenza virus	

Table II: High-risk groups according to South African guidelines

Age	< 5 years and especially < 1 year
Hepatic disease	
Sickle cell anaemia	
Obesity	BMI > 40
Persons < 18 years old on Aspirin therapy	To prevent Reye's syndrome

Table III: Classification of extremely high-risk groups

Extremely high risk	
Age	≥ 85 years
Comorbidities	Multiple comorbidities at any age

Risk stratification is necessary to identify individuals with non-severe influenza who may progress to severe illness. These individuals are categorised into high-risk and extremely high-risk groups, as outlined in Tables I, II, and III.

Additionally, the South African Guidelines identify the individuals listed in Table II as high risk.

Clinical Management

The influenza vaccine remains the cornerstone of management to prevent the complications of influenza, and all high-risk individuals should receive it.

Pregnant women who are vaccinated reduce their own risk of influenza by half, as well as the risk to their infants during the first 24 weeks of life. It is critically important to identify individuals at risk of developing severe influenza in advance. These individuals should be informed to seek medical attention promptly - within 48 hours of symptom onset - to allow for timely initiation of antiviral treatment.

Those classified as extremely high risk should also consult a healthcare provider about prophylactic treatment if they have been exposed to the virus, even before symptoms appear.

Influenza is detected in approximately 7% of children under 5 years of age admitted with pneumonia, and in about 9% of those older than 5 years. Among adults admitted with pneumonia during influenza season, 20–40% test positive for influenza. These findings highlight the importance of testing hospitalised pneumonia patients for influenza and initiating antiviral treatment, such as Oseltamivir, when indicated.

Available antiviral treatment options for Influenza in South Africa:

There are three groups of antiviral therapy available:

1. Neuraminidase inhibitors
   - Oseltamivir (Tamiflu)
   - Zanamivir (Relenza)
2. Cap-snatching endonuclease inhibitor
   - Baloxavir marboxil (Xofluza)
3. M2 ion channel inhibitors
   - Amantadine. Due to the high incidence of resistance, they are no longer advised.

Table IV: Dosage recommendations for patients with normal renal function

Age	Weight	Dose	Duration
Adults	> 40 kg	75 mg bd	5 days
Children 1–12 years	≤ 15 kg	30 mg bd	5 days
	> 15–23 kg	45 mg bd	5 days
	> 23–40 kg	60 mg bd	5 days
	> 40 kg	75 mg bd	5 days
Children < 12 months		3 mg/kg/dose bd (If ≥ 9 months can increase dose to 3.5 mg/kg/dose bd)	5 days

bd = Twice Daily

Neuraminidase inhibitors

Prevent the release and spread of viruses from the cell. They may also prevent attachment and entry into the cell. They are active against influenza A and B viruses.

1. Oseltamivir

Oseltamivir is administered orally, twice daily for treatment and once daily for prophylaxis. In critically ill patients, it can also be administered via a nasogastric tube. While resistance was high during the 2008–2009 seasons, current circulating strains show significantly reduced resistance. It is considered safe for use in pregnancy and can be used in children, although resistance tends to be higher among young children.

Routine use in non-severe influenza is not recommended, as it offers minimal benefit, typically reducing symptom duration by only one day, and does not impact hospitalisation rates or mortality. Additionally, widespread use may contribute to the development of resistance.

However, Oseltamivir is recommended for severe influenza, particularly when initiated within 48 hours of symptom onset. It should also be used in cases of novel influenza A strains with high or uncertain mortality risk, even in patients who are not considered high risk.

That said, the overall benefits in reducing ICU admissions, length of hospital stay, or mortality are limited.

Table VI: Prophylactic dosage recommendations for patients with normal renal function

	Weight	Dosage in severe influenza	Duration of severe influenza	Dosage in Zoonotic influenza	Duration of Zoonotic influenza
Adults	> 40 kg	75 mg daily	10 days	75 mg bd	14 days
Children 1-13yrs	10–15 kg	30 mg daily	10 days	30 mg bd	14 days
	> 15–23 kg	45 mg daily	10 days	45 mg bd	14 days
	> 23–40 kg	60 mg daily	10 days	60 mg bd	14 days
	> 40 kg	75 mg daily	10 days	75 mg bd	14 days
Children < 12 months		3 mg/kg/dose bd (If ≥ 9 months can increase dose to 3.5 mg/kg/dose daily)	10 days	3 mg/kg bd (If ≥ 9 months can increase dose to 3.5 mg/kg/dose daily)	14 days

Table V: Oseltamivir dose adjustments in adults with altered kidney function

CrCl	If the usual indication-specific dose is 75 mg once daily (e.g. seasonal influenza prophylaxis)	If the usual indication-specific dose is 75 mg twice daily (e.g. seasonal influenza treatment)
≥ 60 mL/minute	No dosage adjustment necessary	No dosage adjustment necessary
> 30 to < 60 mL/minute	30 mg once daily	75 mg × 1 dose, then 30 mg twice daily
> 10 to 30 mL/minute	30 mg every other day	30 mg once daily
≤ 10 mL/minute	30 mg once weekly	30 mg every other day

The standard duration of therapy is 5 days; however, in hospitalised or severely ill patients, treatment may be extended, up to 10 days, depending on individual clinical factors.

Prophylactic dose

Oseltamivir may be used as prophylaxis in asymptomatic individuals who are at extremely high risk of developing severe influenza and have been exposed to the virus within the previous 48 hours. In such cases, the dosing is the same as the therapeutic dose but given once daily for 10 days (Table VI). Prophylactic use is not recommended for individuals who are not considered extremely high risk.

For zoonotic influenza infections associated with high or uncertain mortality, Oseltamivir is also recommended as prophylaxis in exposed individuals. In these cases, the treatment dose (twice daily) is used for an extended duration of 14 days.

2. Zanamivir

Zanamivir is administered as a powder for inhalation using a specific inhalation device. It cannot be nebulised. This route of administration may be unsuitable for young children, the elderly, or severely ill patients who are unable to use the device effectively.

Dosage

Treatment dose: 10 mg (two inhalations) every 12 hours for 5 days.

Prophylaxis in extremely high-risk individuals (post-exposure): Same dose, administered once daily for 10 days, starting within 48 hours of exposure.

Prophylaxis for zoonotic influenza (high or unknown mortality risk): Same dose and duration as treatment (10 mg twice daily for 5 days).

Precautions & contraindications

Not recommended for individuals with chronic respiratory conditions such as asthma or COPD, due to the risk of bronchospasm.

Safe for use during pregnancy.

Approved for use in children older than 7 years.

No serious adverse effects have been reported.

Efficacy Considerations

Not recommended for non-severe influenza, as it has minimal impact on symptom duration, hospitalisation rates, or mortality.

Not recommended for severe influenza, as clinical studies have shown no significant benefit in reducing ICU admissions, hospital stays, or mortality.

Endonuclease cap-snatching inhibitor

Baloxavir marboxil *(Registered with SAHPRA but currently not listed at suppliers)*

Baloxavir is a cap-snatching inhibitor that targets the viral endonuclease enzyme. This enzyme allows the virus to "steal" short 5' capped RNA primers from the host's mRNA, which are essential for viral replication. By inhibiting this function, Baloxavir effectively blocks viral replication.

Baloxavir is administered as a carboxyl prodrug, which is hydrolysed into its active form in the body. It has a long half-life with a prolonged tail lasting several weeks, raising concerns about potential development of viral resistance. Therefore, its use is not recommended in immunocompromised patients.

Safety profile

- Pregnancy: Not considered safe, despite animal studies showing no adverse effects at doses five times higher than normal.
- Lactation: No reported adverse effects during breastfeeding.
- Children: Limited data available for use in children younger than 5 years.

Indications for use

Baloxavir is recommended for the treatment of non-severe influenza in individuals at risk of progression to severe illness, including:

- Adults older than 65 years
- Individuals of any age with significant risk factors

Prophylaxis

- Recommended for asymptomatic, high-risk individuals exposed to influenza within the previous 48 hours, specifically those at extremely high risk (e.g. over 85 years old or younger patients with multiple risk factors).
- Also advised for prophylaxis against zoonotic influenza strains with known or uncertain high mortality risks.
- Prophylactic dosing is the same as treatment — a single dose (See Table VII).

Treatment considerations

- Treatment should begin within 48 hours of symptom onset.
- Baloxavir can reduce the duration of illness by approximately one day and may help reduce hospital admissions, although it has not been shown to decrease mortality.
- It is generally well tolerated and not associated with serious adverse events.
- Viral testing before treatment is recommended.

Table VII: Dosage of Baloxavir

Weight	Dose
< 20 kg	2 mg/kg as a single dose (Max: 40 mg)
20–79 kg	40 mg as a single dose
≥ 80 kg	80 mg as a single dose

Adjuvant treatment for Influenza

1. Antibiotic use

In patients with non-severe influenza without secondary bacterial infection, antibiotics are not recommended. The use of Macrolide antibiotics for their anti-inflammatory effects is discouraged, as it can promote antibiotic resistance without reducing symptoms or preventing progression to severe complications like pneumonia.

2. Oxygen therapy

Should be given to keep the SpO2 > 90% and 92–95% in pregnant patients.

3. Use of corticosteroids in severe influenza

Its use is not recommended except for ARDS.

4. Use of NSAIDs in influenza

In non-severe influenza the use of NSAIDs is useful for its symptomatic effect of reducing fever and myalgia. In severe influenza, it is not recommended due to its potential adverse effects on renal function in cases of sepsis and septic shock.

5. Passive immunotherapy

Gamma-globulins are not advised.

Diagnostic strategies for testing for Influenza A.

The following tests are available

Polymerase Chain Reaction **(PCR)** amplifies specific gene sequences and offers high sensitivity and specificity; however, its main limitation is the turnaround time.

Nucleic Acid Amplification Tests **(NAATs)** also provide high sensitivity and specificity for detecting influenza virus nucleic acids, especially when samples are collected within 3–4 days of symptom onset.

Direct Immunoassays **(DIAs)** detect influenza virus antigens with moderate to moderately high sensitivity and high specificity, requiring sample collection within the same 3–4-day window. These tests tend to be less costly. It is advisable to consult with your laboratory regarding the expected turnaround time for test results.

The following management strategies are considered

1. **Treat none** - No test, and do not treat patients with suspected influenza with an antiviral.

2. **Treat all** - No test and treat patients with suspected influenza with an antiviral.

3. **Rapid test and treat** - Test all suspected influenza cases using a rapid point-of-care test (such as NAAT, which has high sensitivity and specificity for detecting influenza viral nucleic acids) and treat only those who test positive.

4. **Test and Treat** - Test all suspected cases with a molecular assay (PCR) and start antiviral treatment immediately while awaiting results (typically within 24 hours). Discontinue treatment if the test result is negative.

5. **Test and Wait** - Test all suspected cases with a molecular assay (PCR) but withhold antiviral treatment until results are available.

How to test

Thanks to the COVID-19 pandemic, most doctors are now skilled at collecting quality nasopharyngeal swabs. Ideally, samples should be taken within the first 3–4 days of symptom onset. When symptoms mainly involve the lower respiratory tract and influenza is suspected, sputum, endotracheal aspirates, or bronchoalveolar lavage specimens can be submitted for NAAT testing.

For patients with non-severe influenza who are at risk of developing severe illness, the recommended approach is to test using NAAT and treat all positive cases with a single dose of Baloxavir (40–80 mg). Oseltamivir and Zanamivir are not indicated for this group.

For patients with severe influenza requiring hospital admission, the recommendation is to test with NAAT and treat only those who test positive with Oseltamivir for 5 days. If PCR testing is available with results within 24 hours, this strategy should be followed: treat only PCR-positive patients with Oseltamivir. If results are delayed beyond 24 hours, a test-and-treat approach may be used initially, but treatment should be stopped if the test result is negative.

In cases where lower respiratory symptoms dominate, the virus may have cleared from the upper respiratory tract, leading to negative swab results. In such situations, testing of lower respiratory specimens with NAAT or PCR is appropriate.

Table VIII: Symptomatic treatment for Influenza

Cough	Dextromethorphan hydrobromide, ammonium chloride and panthenol containing medication as a cough suppressant and an expectorant. Mucolytics – Acetylcysteine containing medication.
Sore Throat	Benzocaine plus Chlorhexidine Gluconate containing solution to gargle, spray or lozenges.
Fever and Myalgia	Paracetamol, Aspirin and Ibuprofen.
Rhinitis	Pseudoephedrine-containing medication.

Summary

Seasonal influenza is upon us, and effective management is essential. Antiviral treatment is not recommended for individuals at low risk of developing severe influenza. Those at risk should receive antivirals, specifically Baloxavir, within 48 hours of symptom onset. In cases of novel influenza A with known or uncertain high mortality, antiviral treatment is also advised, using Baloxavir, Oseltamivir, or Zanamivir.

For patients hospitalised with severe influenza, Oseltamivir is the recommended antiviral. In all situations where treatment is indicated, it is best to test for the virus first and only treat those with a positive result.

Prophylactic antiviral therapy (Baloxavir, Oseltamivir, or Zanamivir) is recommended for individuals at extremely high risk of severe influenza and should be initiated within 48 hours of exposure.

Bibliography

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In my personal view, these guidelines place a significant responsibility on healthcare professionals to identify patients who are at risk or extremely high risk of contracting severe influenza within their practices. It is important that these individuals are informed about their risk status, made aware of the availability of prophylactic treatment, and encouraged to seek medical attention within 48 hours of exposure or symptom onset, since many patients tend to present after this critical window.