NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division in the National Health Laboratory Service

Influenza:

NICD recommendations for the diagnosis, management, prevention and public health response

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Summary of changes:

Date reviewed	Reviewed by	Summary of changes
19 April 2024	**S Walaza**	• Updated influenza vaccine composition for 2024 influenza season • Added summary of 2023 season • Updated section on COVID-19 vaccines
28 April 2023	**S Walaza**	• Updated influenza vaccine composition for 2023 influenza season • Added paragraph on zoonotic influenza • Removed inhaled Zanamivir as a treatment option due to change in WHO guidelines • Added summary of 2022 influenza season • Reduced contagious period for SARS-CoV-2 from at least 7 days to at least 5 days
22 April 2022	S Walaza	• Updated influenza vaccine composition for 2022 influenza season • Guidance on the administration of influenza vaccines with other vaccines has been expanded to include COVID-19 vaccines • Added information on influenza epidemiology • Added information on use of corticosteroids for severely ill patients with influenza and COVID-19
12 April 2021	S Walaza	• Added data on annual national burden of medically and non-medically attended influenza-associated mild, severe-non-fatal and fatal illness among potential target groups in South Africa • Added updated influenza-burden estimates in South Africa

		• Updated influenza vaccine composition for 2021 influenza season • Updated information on quadrivalent influenza vaccine • Added section on administration of influenza vaccine and SARS-CoV-2 vaccine • Added procedures for collecting mid-turbinate nasal swabs • Added information on influenza and SARS-CoV-2 co-circulation and implications for testing and public health response • Added summary of influenza and COVID-19 clinical presentation
2 April 2020	J Moyes	Updated influenza vaccine composition for 2020 influenza season Updated groups recommended to receive vaccine New guidance on influenza vaccine and COVID and quadrivalent influenza vaccines
6 June 2019	S Walaza	Updated influenza vaccine composition for 2019 influenza season
13 April 2018	S Walaza	Updated influenza vaccine composition for 2018 influenza season Updated influenza burden estimates

Disclaimer:

The information contained in this document, be it guidelines, recommendations, diagnostic algorithms or treatment regimens, is offered in the public interest. To the best of the knowledge of the writing team, the information contained in these recommendations is correct at the time of publication. Implementation of any aspect of these guidelines remains the responsibility of the implementing agency in so far as public health liability resides, or the responsibility of the individual clinician in the case of diagnosis or treatment.

Quick Reference Guide - Influenza

Categories of influenza- Page 9

Uncomplicated influenza: ILI (Influenza-like illness) may present with fever, cough, sore throat, coryza, headache, malaise, myalgia, arthralgia and sometimes gastrointestinal symptoms, but without any features of complicated influenza.

Complicated influenza: Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, tachypnoea, lower chest wall indrawing and inability to feed), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

Risk groups for severe/complicated influenza disease - Page 10-11

- Pregnant women and women up to 6 weeks postpartum
- People living with HIV
- Individuals with tuberculosis
- Persons of any age with chronic diseases:
  - Pulmonary diseases (e.g. asthma, COPD)
  - Immunosuppression (e.g. persons on immunosuppressive medication, malignancy)
  - Cardiac diseases (e.g. congestive cardiac failure), except for hypertension
  - Metabolic disorders (e.g. diabetes mellitus)
  - Renal disease
  - Hepatic disease
  - Neurologic and neurodevelopmental conditions
  - Haemoglobinopathies (e.g. sickle cell disease)
- Persons aged ≥65 years
  Persons ≤18 years receiving chronic aspirin therapy
- Persons who are morbidly obese (i.e. BMI ≥40).
- Young children (particularly <2 years of age)

Treatment of influenza - Page 17-19

Neuraminidase inhibitor (oseltamivir) recommended for the treatment of any patient with suspected or confirmed influenza who:

- has complicated or severe illness (including all hospitalised patients)
- is at higher risk for influenza complications

Treatment should be started early, ideally within 48 hours of symptom onset.

Groups targeted for Department of Health 2024 influenza vaccination campaign - Page 21, in order of priority

- Healthcare workers
- Individuals aged ≥65 years
- Individuals with cardiovascular disease (including chronic heart disease, hypertension, stroke and diabetes), chronic lung disease (including asthma and chronic obstructive pulmonary disease) and individuals with immunosuppressive conditions (e.g. living with HIV and AIDS and malignancy)
- Pregnant women

Recommended inactivated influenza vaccine (IIV) formulation for 2024 - Page 19, 20

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/ Thailand/8/2022 (H3N2)- like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage) like-virus; and
- B/Phuket/3073/2013-like (B/Yamagata lineage) virus*

*included in the quadrivalent vaccine, available in private sector

Dosage of influenza vaccine - Page 22

- ≥ 9 years –0.5ml IMI single dose (TIV/QIV)
- 3 years to 8 years - 0.5ml IMI 1 or 2 doses (TIV/QIV)*
- 6 months to 2 years - 0.25ml IMI 1 or 2 doses (TIV)*
- 6 months to 2 years - 0.5ml IMI 1 or 2 doses (QIV)*

*2 doses should be administered ≥ 1 month apart during 1st year of vaccination, thereafter one dose.

IMI-intra-muscular injection, QIV-quadrivalent influenza vaccine, TIV-trivalent influenza vaccine

Additional questions from health professionals can be directed to: for clinical support - National Institute for Communicable Diseases (NICD) **Hot line**: 080 021 2552, for laboratory support - NICD, Centre for Respiratory Diseases and Meningitis: **011 386 6410** sibongilew@nicd.ac.za| cherylc@nicd.ac.za|nicolew@nicd.ac.za

1. Introduction

Seasonal influenza

Influenza, commonly known as the "flu", is an acute infection of the respiratory tract caused by influenza viruses. There are three types of seasonal influenza viruses – A, B and C. Influenza A viruses are further categorised into subtypes, and influenza B into lineages. The 2009 pandemic influenza A(H1N1) virus (hereafter referred to as influenza A(H1N1)pdm09) which appeared for the first time in 2009 causing a global influenza pandemic, is now a seasonal influenza virus that co-circulates with other seasonal viruses (namely influenza A(H3N2) and influenza B viruses). Influenza viruses are genetically dynamic and evolve in unpredictable ways. Influenza viruses are further classified based upon antigenic properties. Humoral immunity to influenza viruses is generally thought to be strain-specific and acquired through infection and/or vaccination. Seasonal influenza epidemics can be caused by evolving virus strains that are antigenically distinct from previously circulating virus strains to which a population has some immunity; this is known as antigenic drift. Uncommonly, a completely new strain of influenza will emerge to which there is little or no existing immunity, this is known as antigenic shift and such novel strains can give rise to influenza pandemics.

Zoonotic influenza

Influenza viruses circulating in animal species 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) can sporadically be transmitted to humans, causing mild to very severe disease and may contribute to the emergence of pandemic strains. Human infections are primarily acquired through direct contact with infected animals or contaminated environments. Human infection can range from asymptomatic to conjunctivitis or mild upper respiratory tract illness (cough with or without fever) to rapid progression to severe pneumonia, acute respiratory distress syndrome (ARDS, multi-organ failure, sepsis with shock and even death. Currently, zoonotic influenza is rare as it requires close contact with animals such as pigs or birds, and human-to-human transmission of zoonotic influenza is very uncommon. Additional information on avian influenza can be accessed here Avian influenza guidance.

2. Epidemiology

Influenza virus infections cause substantial annual morbidity and mortality worldwide, including South Africa [1-4]. Annual influenza epidemics result in an estimated three to five million cases of severe illness, and about 290 000-650 000 deaths globally[4]. Influenza is an important cause of

pneumonia or lower respiratory tract infection (LRTI) and approximately 8-10% of all patients with pneumonia test positive for influenza [5].

The burden of influenza in sub-Saharan Africa (and specifically in South Africa) is substantial, with some studies suggesting elevated influenza-associated mortality rates compared to other regions [6, 7]. During the influenza season (usually between May and September) in South Africa, approximately 14% of inpatients with lower respiratory tract infection and 25% of patients with influenza-like illness will test polymerase chain reaction (PCR) positive for influenza. A modelling study from South Africa using case-based and ecological data estimated that during 2013-2015 on average 10 737 847 (19.8%) South Africans had influenza-associated illness annually of which 10 598 138 (98,7%) were mild, 128 173 (1,2%) were severe and 11 536 (0.1%) were fatal.[8] The highest number of mild cases occurred among individuals aged 5–24 years (5 745 544, 54.2%). An estimated 4 195 (36.1%) of influenza-associated deaths were in individuals aged ≥65 years. Overall, the rates of influenza-associated mild illness were highest among individuals aged 5-24 years (28 935.2 per 100 000 individuals in the population), rates of influenza-associated severe non-fatal illness were higher among individuals aged <1 year (1550.9 per 100 000 individuals in the population) and ≥65 years (761.3 per 100 000 individuals in the population), and rates of influenza-associated deaths were higher among infants<1 year (80.3 per 100 000 individuals in the population) and persons aged ≥65 years (137.9 per 100 000 individuals in the population)[8]. In South Africa, among individuals aged ≥5 years, an estimated 30% of influenza-associated deaths are in People living with HIV (PLWH) [9]. Pregnant women also constitute an important risk group for influenza-associated mortality. Among an estimated 646 - 1 428 seasonal influenza-associated deaths in women of childbearing age in South Africa, the majority (~90%) occurred in PLWH and the influenza-associated mortality was three-fold higher (relative risk (RR) 2.8, 95% confidence interval (CI) 1 .7 – 3.9) in pregnant compared with non-pregnant women. [10]

The highest rates of influenza-associated hospitalisation are in those aged ≥65 years, PLWH and children aged <5 years (in particular children <1 year). [1, 9, 11-13]. Data from South Africa showed that extremes of age (<6 months [adjusted odds ratio (aOR), 37.6], 6–11 months [aOR, 31.9], 12-23 months [aOR, 22.1], 24–59 months [aOR, 7.1], and ≥65 years [aOR, 40.7] compared to those aged 5-24 years), underlying medical conditions (aOR, 4.5), HIV infection (aOR, 4.3) and history of working in a mine (aOR, 13.8) were significantly associated with increased risk of influenza associated hospitalisation [14]. Influenza infection may trigger exacerbations of diabetes, pulmonary (e.g. asthma) or cardiovascular disease. For this reason, people with underlying chronic medical

conditions are at high risk of influenza complications, often resulting in hospitalisation and even death. Surveillance data from South Africa showed that having underlying illnesses (other than HIV) was a risk for influenza-associated mortality (odds ratio (OR) 2.9, 95% CI 1.2 - 7.3) [1]. Individuals with tuberculosis may also be at increased risk of influenza-associated death [15, 16]. The burden of hospitalisations and deaths due to influenza can vary substantially from year to year depending on the transmission and virulence characteristics of the circulating strain(s).

A recent study in South Africa, assessing the mean annual national burden of medically and non-medically attended influenza-associated mild, severe-non-fatal and fatal illness among potential target groups for influenza immunisation in South Africa during 2013-2015, reported that rates of influenza-associated illness were highest in children aged 6-59 months (23,983 per 100,000 population) for mild illness, in pregnant women (930 per 100,000 population) for severe-non-fatal illness and in individuals aged ≥65 years (138 per 100,000 population) for fatal illness.[17]

In tropical areas, influenza occurs throughout the year. In temperate areas, like in South Africa, influenza is highly seasonal and typically occurs during winter months. In 2023, the influenza season which started in week 17 (week starting 24 April 2023) and ended in week 27 (week starting 10 July) was predominated by influenza A(H3N2), with influenza B/Victoria predominating in the last few weeks of the season.

Microbiology, pathology and pathogenesis

Human influenza viruses are single-strand RNA viruses that belong to the Orthomyxoviridae family, consisting of the genera influenza A, B, and C viruses. Only influenza A and B viruses cause epidemics in humans. Based on their main antigenic determinants, the haemagglutinin (H or HA) and neuraminidase (N or NA) transmembrane glycoproteins, influenza A viruses are further subdivided into 18 H (H1–H18) and 11 N (N1–N11) subtypes, but only 3 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.

HA and NA are critical for pathogenesis, and are major targets for the neutralizing antibodies of acquired immunity to influenza.

3. Transmission

Influenza viruses are spread from person-to-person. They can be transmitted by exposure to infectious droplets expelled by coughing or sneezing that are then inhaled by others, or can contaminate hands or other surfaces. The typical incubation period for influenza is 1-4 days (average

2 days). Most persons ill with influenza shed virus (i.e. may be infectious) from a few days before symptoms begin through 5-7 days after illness onset. However, very young children can be infectious for >10 days after illness onset; adults with severe disease (e.g. viral pneumonia) may also shed virus for >10 days, and severely immunocompromised persons can shed virus for even longer [18]. Children have the highest rates of seasonal influenza infection and illness in this group can amplify viral transmission in the community.

4. Clinical presentation and risk factors for influenza

Infection with influenza viruses has a wide range of clinical presentations, ranging from asymptomatic infection to severe illness and death depending on the characteristics of both the virus and the infected person. In the majority of people, influenza is an uncomplicated illness that is characterised by sudden onset of constitutional and respiratory symptoms such as fever, myalgia, cough, sore throat, rhinitis and headache. Uncomplicated influenza illness resolves after 3-7 days, although cough and malaise can persist for >2 weeks. Influenza may be associated with more severe complications including: influenza-associated pneumonia/ LRTI, secondary bacterial or viral infection (including pneumonia, sinusitis and otitis media), multi-organ failure, and exacerbations of underlying illnesses (e.g. pulmonary and cardiac illness). Rare complications include encephalopathy, encephalitis, transverse myelitis, myocarditis, pericarditis and Reye syndrome. For purposes of clinical management, influenza disease can be categorised as follows [19]:

- **Uncomplicated influenza:** ILI (Influenza-like illness) may present with fever, cough, sore throat, coryza, headache, malaise, myalgia, arthralgia and sometimes gastrointestinal symptoms, but without any features of complicated influenza.
- **Complicated/severe influenza:** Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, tachypnoea, lower chest wall indrawing and inability to feed), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

4.1 Risk factors for complicated/severe influenza

Certain groups of patients are at higher risk of developing severe or complicated disease following influenza virus infection. However, influenza virus infection can result in severe/complicated illness in previously healthy individuals. Similar to other studies showing increased risk of severe influenza-associated illness in certain individuals, [1, 2, 6, 9, 10, 15, 16, 20, 21] a study from South Africa found that younger and older age (<5 years, in particular children <1 year, and ≥65 years) and the presence of

chronic underlying medical conditions, HIV infection and pregnancy were associated with increased risk of influenza-associated hospitalisation[14]. In addition, PLWH with severe immunosuppression compared to those with mild immunosuppression had three times increased odds of influenza-associated hospitalisation [14].

4.1.1 Risk groups for severe/complicated influenza disease include:

- Pregnant women and women up to 6 weeks postpartum
- People living with HIV [14, 22]
- Individuals with tuberculosis[15, 16, 23]
- Persons of any age with chronic disease, including:
    - Pulmonary diseases (e.g. asthma, COPD)[24]
    - Immunosuppression (e.g. HIV, persons on immunosuppressive medication, malignancy)
    - Cardiac diseases (e.g. congestive cardiac failure), except for hypertension[24]
    - Metabolic disorders (e.g. diabetes mellitus)[25]
    - Renal disease
    - Hepatic disease
    - Certain neurologic and neurodevelopmental conditions, including: disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, mental retardation, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury.
    - Haemoglobinopathies (e.g. sickle cell disease)
- Persons aged ≥65 years
- Persons aged ≤18 years receiving chronic aspirin therapy
- Persons who are morbidly obese (i.e. BMI ≥40)[26]
- Children aged <5 years (particularly <1 years of age)

4.1.2 Groups at increased risk for severe influenza illness and COVID-19

There is some overlap in the groups of individuals who are at increased risk for severe influenza illness or complications and severe COVID-19. To ensure optimal control of influenza among these groups, it is essential that these groups are prioritized for influenza vaccination. Groups of individuals at increased risk for both severe influenza illness and severe COVID-19 include:

- Persons aged ≥65 years

- Persons of any age with underlying chronic diseases, notably diabetes
- People living with uncontrolled HIV or with other comorbidities that cause immunosuppression
- Persons who are morbidly obese (i.e. BMI ≥40)
- Pregnant women

5. Laboratory Diagnosis

Laboratory testing of uncomplicated illness (patients who fit the ILI case definition) is **NOT** routinely recommended, as it provides no advantage in the management of individual patients. Testing can be considered for the following patients:

- Patients who meet the criteria for complicated or severe influenza, where a laboratory diagnosis will assist in patient management.
- Clusters of cases where a diagnosis of the cause of the outbreak is needed (e.g. within institutions such as healthcare facilities, nursing homes). First 2-3 cases to be tested, thereafter testing not required.

Important note: **Initial treatment decisions should be based on clinical presentation and should NOT be delayed pending laboratory confirmation of influenza.**

These recommendations for laboratory testing do not apply to surveillance activities (e.g. Viral Watch, influenza-like illness (ILI), pneumonia surveillance programme), and testing should continue as guided by those individual surveillance programmes.

5.1 Laboratory testing for influenza

The NICD does not offer routine diagnostic testing, including for influenza, outside of established surveillance programmes at specific sites. Diagnostic capacity to test for influenza viruses is established in various National Health Laboratory service (NHLS) and private-sector laboratories throughout the country. Under special circumstances (e.g. outbreak investigation), NICD will provide support for testing. Requests for testing at NICD should be discussed with the doctor on call, through the **NICD Hotline –**0800 21 2552 before samples are collected.

In line with WHO recommendations, molecular diagnostics (real-time multiplex PCR for influenza A and B virus or Gene Xpert® for influenza A and B virus) are currently the method of choice for influenza virus detection. While specificity is high, the sensitivity of currently available rapid-point-

of-care or immunofluorescence tests designed for direct detection of influenza A viruses is low (59%-93%) and therefore they are not recommended for diagnostic purposes. A negative Rapid Influenza Diagnostic Test (RIDT) result does NOT exclude influenza infection, and should not preclude starting empiric antiviral treatment where clinical indications exist.

Where influenza and SARS-CoV-2 coinfection is suspected in a hospitalised patient, multiplex assays for simultaneous detection of influenza viruses and SARS-COV-2 may be used when available. For patients presenting with mild symptoms, only testing for SARS-CoV-2 is required, as the influenza result is not going to influence management. Current testing guidelines for SARS-CoV-2 require that symptomatic patients suspected of COVID-19 be tested using either a rapid antigen test or PCR (follow link, Testing). Laboratory-confirmed cases of SARS-CoV-2 infection need to be notified to the notifiable medical conditions (NMC) surveillance system, either through the online application (follow link, NMC) or by paper form submitted to the NMC.

5.2 Diagnosis of influenza and COVID-19 when SARS-CoV-2 and influenza viruses are co-circulating

Because COVID-19 and influenza may present the same way, during the expected influenza season, it may be necessary to do an influenza test in addition to SARS-CoV-2 test if influenza test results would inform clinical management and public health response. In addition, among hospitalised patients, depending on clinical presentation, testing for other viral and bacterial pathogens causing severe respiratory illness should be considered, in particular in patients with influenza in whom bacterial superinfection is a well-described complication.

5.3 Specimen collection, storage and transportation

Combined nasopharyngeal and oropharyngeal swabs in universal transport medium (UTM) are the preferred specimens for testing. However, when aerosolisation of respiratory samples is to be avoided and/or swabs are limited, a mid-turbinate nasal swab or oropharyngeal swab in place of a nasopharyngeal swab can be used. Flocked swabs should be used to collect specimens as they provide a better yield on PCR [27]. Dacron or rayon swabs may be used if flocked swabs are not available. Cotton wool budded swabs are not recommended. Once collected, these samples should be placed in viral or universal transport medium and transported on cooler box with ice packs to the testing laboratory. The specimens must be refrigerated at 2-8°C if transport is expected to be delayed. If the specimen(s) cannot be shipped within 72 hours of collection, they should be kept frozen at -20°C. Avoid repeated freezing and thawing of specimens.

For specimens submitted to NICD to test for influenza, a completed specimen request form (follow link, CRDM-specimen-submission-form) with patient name, health facility (where appropriate), healthcare worker's name and contact numbers, laboratory name, contact person, telephone, fax number and email address for receipt of results, and clinical details should accompany the sample. For suspected avian influenza a specimen submission form AND avian influenza case investigation form should be completed, forms available here, (follow link Avian influenza)

5.3.1 Additional considerations for sample collection

- Specimens for virus isolation or for detection of viral nucleic acids or antigens should preferably be collected within three days of onset of symptoms, but may be taken up to a week after onset or even later in children, severely ill or immunocompromised patients.
- Specimens should preferably be taken prior to commencement of antiviral therapy but can still be taken a few days after initiation, especially in patients who are deteriorating on antiviral treatment. In these cases, antiviral resistant infection should be considered and testing for oseltamivir resistant virus may be considered.
- In addition to swabs from the upper respiratory tract, invasive procedures such as bronchoalveolar lavage/bronchial aspirate or lung biopsy can be performed for the diagnosis of influenza where clinically indicated. Expectorated and induced sputum can also be tested. However, it is important to note that aerosolising procedures should be avoided, where SARS-CoV-2 infection is suspected.
- Results of all diagnostic tests for influenza are dependent upon several factors (including specimen type and quality of specimen collection, timing of collection, storage and transport conditions), such that false-negative results may be obtained. When clinical suspicion is high, clinicians can consider repeat/serial testing. Lower respiratory tract specimens may yield the diagnosis when testing of upper respiratory tract specimens is negative. Multiple respiratory tract specimens collected on different days can be tested if proof of influenza infection is important/needed.

5.3.2 Procedure for sample collection

A respiratory specimen (ideally, combined nasopharyngeal swab and oropharyngeal swab or aspirate, but a mid-turbinate nasal or oropharyngeal swab where combined sample is not possible) should be collected. Caution should be taken when collecting a nasopharyngeal swab or aspirate as these can cause aerosolisation of respiratory particles. In small children it may be easier and less

traumatic to collect an aspirate rather than nasopharyngeal swab but both specimen types are acceptable and have similar diagnostic yield[28].

- Carefully label the vial of UTM with patient identification information and date of specimen collection
- Gently insert the flocked swab through one nostril beyond the anterior nares along the floor of the nasal cavity, until the pharyngeal wall is reached (swab to reach depth equal to distance from nostril to outer opening of ear)
- Do not use more than minimal force if any obstruction is encountered
- Rotate the swab three times against the nasopharyngeal wall and then withdraw the swab slowly
- Place the swab into UTM without touching it, snap off the tip at the marked break point
- Secure the cap
- Transport the labelled swab to the laboratory

Mid- turbinate nasal swab

- Open nasal swab: remove the nasal swab from the wrapper by pulling the two ends of the wrapper apart. Be careful to only touch the handle, not the tip (Figure 1).

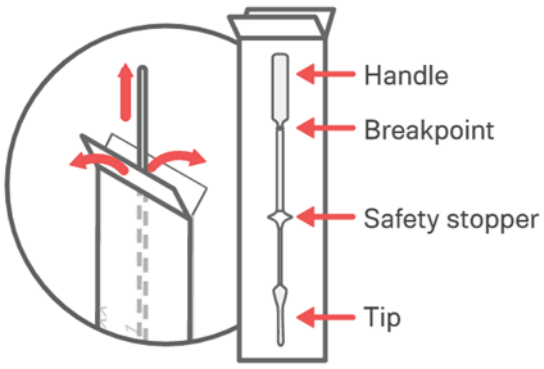

Figure 1: Nasal swab

- Loosen cap on tube: slightly loosen the cap from the tube so it's easier to open later. Place it in a safe location where it won't spill – there is liquid inside (you'll be putting your swab into this tube when finished) (Figure 2).

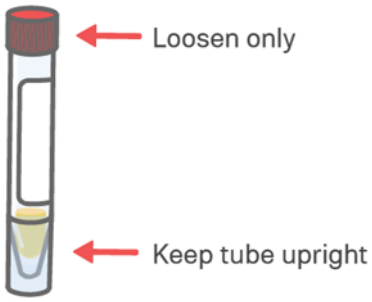

Figure 2: Specimen collection tube

- Swab nose: Tilt head back to look at ceiling, and gently insert the soft tip of the swab into one nostril until the safety stopper touches the edge of the nostril. Gently twist the handle in a circular motion for 15 seconds. Next, gently insert the same swab into the other nostril and repeat the same 15-second procedure (Figure 3).

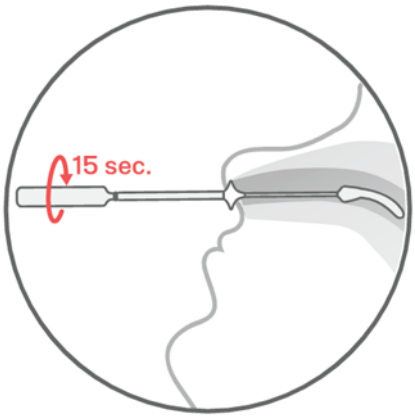

Figure 3: Sample collection

- Put swab in tube: Lower the swab, tip first, into the provided tube. Once the tip is at the bottom, break the swab handle at the swab breakpoint by bending back and forth. Screw the cap on tightly (Figure 4).

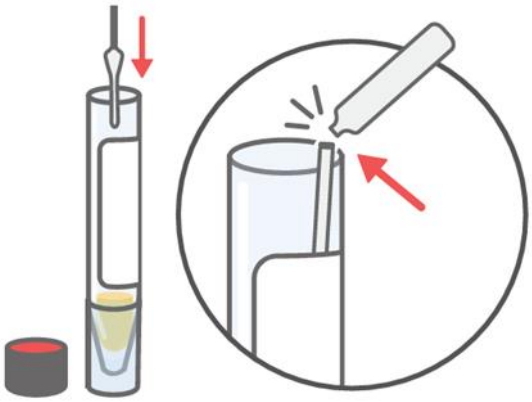

Figure 4: Putting swab in tube

Transport of samples to NICD

For samples that are going to be tested at NICD (see section 5.1 and 5.3), specimens should be transported within 24 hours to the Centre for Respiratory Diseases and Meningitis (CRDM), National Institute for Communicable Diseases (NICD), 1 Modderfontein Road, Sandringham, 2131. Please complete specimen submission form: click link CRDM-specimen-submission-form

6. Clinical management and considerations for treatment of influenza

Influenza is detectable in approximately 7% of children aged <5 years hospitalised with pneumonia and 9% of individuals aged ≥5 years hospitalised with pneumonia in South Africa. [29, 30]. During the influenza season, this increases to approximately 20-40% of all adults hospitalised for pneumonia. For this reason, influenza must be considered as an important potential cause of community acquired pneumonia (CAP) in all patients during the influenza season or when there is increased influenza transmission in the community and consideration must be given to including oseltamivir as part of empiric treatment where indicated (see section 6.1) and available. Note that because influenza vaccination is not 100% effective, a history of influenza vaccination does not exclude the possibility of influenza infection in patients with compatible clinical features.

6.1 Antiviral therapy

Antiviral medications with activity against influenza are an adjunct to influenza vaccine in the control of influenza. Few patients with influenza require treatment and initiation of treatment should be based on clinical judgment taking into consideration the patient's disease severity and progression, age, underlying medical conditions, likelihood of progressing to severe influenza, and time since onset of symptoms. When indicated, antiviral treatment should be started as early as possible, ideally within 48 hours of symptom onset, and should not be delayed while awaiting laboratory confirmation. However, antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness, and in hospitalised patients when started more than 48 hours after illness onset. Antiviral therapy is recommended as early as possible for any patient with confirmed or suspected influenza who

- has complicated or severe illness (including all hospitalised patients), or
- has higher risk for influenza complications (see section 4.2.1).

Antiviral treatment is not indicated for treatment of influenza in persons who do not fall in the risk groups for severe influenza-associated disease and who present with uncomplicated influenza.

Prospective, randomised, controlled clinical trials (RCTs) show that treatment with oseltamivir for uncomplicated influenza illness can reduce the duration of symptoms by approximately 1 day when given within 48 hours of onset of illness [31-34] . Because of the large sample sizes required, there have not been RCTs conducted specifically to evaluate the effect of oseltamivir against severe outcomes such as hospitalisation or death. Observational data suggest a benefit of oseltamivir treatment against severe outcomes, although these may be subject to several limitations. A meta-analysis of individual patient data reported lower risk of mortality in patients treated with neuraminidase inhibitors compared to those not treated.[35] A meta-analysis showed a risk reduction in lower respiratory tract complications and in-hospital stay in the group that received oseltamivir [36]. For this reason, the South African guidelines continue to recommend the use of neuraminidase inhibitors for the treatment of hospitalised patients with confirmed or suspected influenza who have complicated or severe influenza or are at higher risk for influenza complications (see section 4.2.1).

6.1.1 Recommended antiviral medication

Oral oseltamivir (Tamiflu®) and inhaled zanamivir (Relenza®) (limited availability in South Africa) are chemically related antiviral medications that act as neuraminidase inhibitors and have activity against both influenza A and B. Oseltamivir is recommended for use during the 2024-influenza season/ or periods of increased influenza transmission in the community. The WHO no longer recommends zanamavir due to lack of evidence of benefit (or harm) against influenza severe disease. Adamantanes (amantadine and rimantadine) are not recommended for use due to high levels of resistance. The standard adult dose and duration of oseltamivir treatment is 75mg twice daily orally for 5 days. Doses for treatment are summarised in Table 2 [37].

6.1.2 Antiviral treatment of influenza when influenza viruses and SARS-CoV-2 are co-circulating

Treatment for influenza is the same for all patients regardless of SARS-CoV-2 co-infection. For hospitalised patients with suspected influenza illness, empiric treatment for influenza with oseltamivir should be started as soon as possible without waiting for influenza testing results. Oseltamivir has no activity against SARS-CoV-2.

Table 2: Recommended dosage and duration of influenza antiviral medications for treatment

Antiviral Agent	Children	Adults

Oseltamivir (Tamiflu®)	**Neonates and infants (**1 day -12 months) 3mg/kg twice a day for 5 days	75 mg **twice** daily for 5 days
	If ≥ 1 year, dose varies by child's weight ≤15 kg, the dose is 30 mg **twice** a day for 5 days >15 to 23 kg, the dose is 45 mg **twice** a day for 5 days > 23 to 40 kg, the dose is 60 mg **twice** a day for 5 days >40 kg, the dose is 75 mg **twice** a day for 5 days	

Other issues regarding critical care management of patients with influenza are beyond the scope of this document. A comprehensive review appears in the journal *Critical Care Medicine* 2010 Vol. 38, No. 4(Suppl.) pp e1-e142: H1N1 Novel Influenza: Pandemic Issues for Critical Care Practitioners. Free access is available online at: http://journals.lww.com/ccmjournal/toc/2010/04001

6.2 Other interventions for management

Antibiotic treatment: Antibiotics do not have a specific effect against the influenza virus but in cases of pneumonia, early empiric treatment for community-acquired pneumonia is advised because of the high risk of secondary bacterial infection. Since there is increased risk of secondary infection with *Streptococcus pneumoniae, Staphylococcus aureus* and *Streptococcus pyogenes,* co-amoxiclav is a suitable empiric antibiotic.

Oxygen therapy: Monitor oxygen saturation and maintain SaO2 >90% (92-95% for pregnant women) with nasal cannulae or face mask. High flow oxygen treatment may be required in severe cases of influenza.

Corticosteroids: Corticosteroids are not recommended for the sole indication of suspected or confirmed influenza virus infection with or at risk of severe illness. Data from observational studies, although of low quality, showed a signal of increased mortality in influenza infection treatment with steroids[38, 39]. Currently, no data are available on the use of corticosteroids in patients with SARS-CoV-2 and influenza virus coinfection. However, since dexamethasone has demonstrated substantial benefits for patients with COVID-19 pneumonia requiring supplemental oxygen, the benefits of using corticosteroids in patients with severe SARS-CoV-2 and influenza virus coinfection likely outweigh any potential harms.

7. Prevention of influenza

Influenza vaccination is the most effective method for prevention and control of influenza infection available currently. In general, influenza vaccines are most effective among children aged ≥2 years

and healthy adults. A meta-analysis including data from years when there was a mismatch between vaccine and circulating strains estimated a pooled vaccine efficacy (VE) of 59% (95% CI: 51-67) in healthy adults.[40] Previous studies from South Africa have reported influenza VE estimates from 2005 to 2015 which ranged between 46% and 87% when there was a good match and ranged between -14% and 38% when the circulating A(H3N2) strain showed marked genetic drift [41, 42]. A randomised controlled trial conducted in South Africa has shown that when pregnant women received the influenza vaccine, their risk of developing influenza was halved, as was the risk to their infants in the first 24 weeks of life [43]. The vaccine has been shown not only to be efficacious for prevention of influenza in both mothers and their infants, but also safe.[44-46]. Trivalent influenza vaccine has been shown to provide protection in adults living with HIV without severe immunosuppression [47]. Data are unclear as to the effectiveness in HIV-infected children aged <5 years [48]. In certain groups, including the elderly, immunocompromised individuals and infants, influenza vaccine is less effective; however, it may reduce the incidence of severe disease, e.g. bronchopneumonia, hospital admission and mortality.

7.1 Influenza vaccination

Because of the changing nature of influenza viruses, WHO continuously monitors the epidemiology of influenza viruses circulating throughout the world. Each year recommendations about strains to be included in the vaccine for the upcoming influenza season are made. Separate recommendations are made for the Southern and Northern Hemisphere vaccines each year[49]. It is highly likely that co-circulation of influenza and SARS-CoV-2 will occur. Above average coverage of influenza vaccination may assist with reducing the number of people requiring hospitalisation. Groups at increased risk for severe influenza illness and COVID-19, listed in section 4.2.2 above, should be prioritised for influenza vaccination.

7.1.1 Recommended influenza vaccine formulation for 2024

The following strains have been recommended for the trivalent and quadrivalent inactivated influenza vaccine (IIV) 2024 Southern Hemisphere influenza season [49]:

Egg-based tri/quadri-valent vaccines

- an A / Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/ Thailand/8/2022 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage) like- virus; and
- a B/Phuket/3073/2013-like (B/Yamagata lineage) virus*.

*Quadrivalent vaccine is available in private sector.

These recommendations include a change to the A(H1N1)pdm09 and the A(H3N2) component of egg-based vaccines strains compared with the 2023 Southern Hemisphere trivalent and quadrivalent IIV. For the A(H1N1)pdm09 vaccine virus component, the A/Sydney/5/2021-like virus was replaced with A/Victoria/4897/2022-like viruses. For the A(H3N2) vaccine component, the A/Darwin/6/2021-like virus was replaced with A/Thailand/8/2022 (H3N2)-like virus. The WHO recommended trivalent IIV is available in the public sector (at designated clinics and hospitals). The quadrivalent IV is available in the private sector, generally from March or April. Either trivalent- or quadrivalent- IIV may be used during 2024 depending on cost and availability at the time.

7.1.2 Quadrivalent influenza vaccine

Quadrivalent IIV in South Africa was first introduced in the private sector in 2020, and in 2021 and 2022 it was available in the private and public sector, although limited doses were available in the latter. Quadrivalent IIV differs from trivalent IIV in that it provides active immunisation against four influenza virus strains (two A subtypes and two B lineages) compared to trivalent IIV which contains two A subtypes (influenza A(H1N1)pdm09 and influenza A(H3N2) and a single B lineage (either B Victoria or Yamagata lineage). As influenza B Yamagata has not circulated for a number of years, the WHO is recommending use of trivalent vaccines.

7.1.3 Preventing seasonal influenza during a period with SARS-CoV-2 co-circulation

Non-pharmaceutical interventions to prevent transmission of both influenza and SARS-CoV-2 should be promoted and influenza vaccination especially among groups at high risk of severe influenza illness and COVID-19 should be promoted.

7.1.4 Influenza vaccination and COVID-19

Influenza vaccination has no known efficacy against SARS-CoV-2. However, the signs and symptoms of influenza are similar to those of COVID-19. If available, influenza vaccination is recommended to decrease the chances of getting influenza during the winter, when influenza and SARS-CoV-2 may both circulate. It is particularly important to protect healthcare workers and ensure they are able to work and to reduce additional burden on the health system.

7.1.5 Groups recommended for influenza vaccination

Because of limited resources and the fact that not all individuals who fall among the groups at risk for severe influenza disease respond well to influenza vaccination, the National Department of Health is prioritizing certain groups of individuals. The recommendation for groups to be prioritised will be reviewed annually based on available data and resources. Prioritisation strategy for 2024 has taken into consideration the COVID-19 epidemic. The following are among the groups that are prioritised for the targeted public-funded influenza vaccination campaign in 2024, these priority groups apply to both public funded vaccine and privately accessed vaccine:

- Healthcare workers
- Individuals aged ≥65 years
- Individuals with chronic cardiovascular disease (including chronic heart disease, hypertension and stroke), diabetes, chronic lung disease (including asthma and chronic obstructive pulmonary disease) and individuals with immunosuppressive conditions (e.g. living with HIV or AIDS and malignancy).
- Pregnant women at all stages of pregnancy, including women up to 6 weeks postpartum

Other groups that would benefit from influenza vaccination should adequate vaccines supplies be available once the above groups have been vaccinated:

- Individuals (adults or children ≥6 months) who are at high risk for influenza and its complications because of underlying medical conditions and who are receiving regular medical care for conditions including tuberculosis, chronic renal disease and metabolic disorders such as inherited metabolic disorders and mitochondrial disorders.
- Residents of old-age homes, chronic care and rehabilitation institutions.
- Persons aged 6 months to ≤18 years on long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection.
- Individuals who are morbidly obese (body mass index ≥40 kg/m^2).
- Adults and children who are family contacts of individuals at high risk of severe influenza.
- Any persons wishing to minimise the risk of influenza acquisition, especially in workplace settings where large-scale absenteeism could cause significant economic losses.

Healthcare workers should also advise/inform patients where influenza vaccines are provided free of charge or provided as part of their annual medical aid benefits.

7.1.6 Contraindications to influenza vaccination

The IIV is an inactivated vaccine, and has a well-established safety record. It is safe for use in pregnancy and in children ≥6 months of age. Contraindications to the administration of IIV include:

- A history of severe (anaphylactic) hypersensitivity to any component of the vaccine, including egg protein, or after a previous dose of any influenza vaccine. Anaphylaxis is rare and a careful history will distinguish between anaphylaxis and other allergic reactions. Mild egg protein allergy is not a contraindication to influenza vaccine.
- Infants <6 months of age

Precautions

- Persons with moderate illness with or without fever should preferably be immunised after symptoms have resolved.

7.1.7 Influenza vaccine dosage and administration

Influenza vaccine should be given sufficiently early to provide protection for the coming winter. A protective antibody response takes about 2 weeks to develop. The best time to vaccinate is before the influenza season starts, but getting it later will still protect during the rest of the season. Since influenza can circulate in the community outside the normal influenza season, it is never too late to vaccinate. Vaccination should continue to be offered as long as influenza viruses are circulating and a valid vaccine (before expiration date) is available.

The IIV should be administered intramuscularly (IM) as follows:

- Adults and children aged ≥6 years: Injection into the upper arm (deltoid). An opposite arm should be used for other vaccines (COVID-19) administered on the same visit.
- Children aged 1 year to <6 years: Injection into the LEFT upper arm
- Infants aged 6 months – <1 year: Injection into the LEFT antero-lateral thigh

Table 3: Recommended dosage of influenza vaccine

Age Group	Dose	Number of doses
Adults and children 9 years of age and older	Adult dose (0,5ml) IMI	Single dose
Children 3 years through 8 years	Adult dose (0,5ml) IMI	1 or 2 doses[†]
Children 6 months through 2 years	TIV 0,25ml (half the adult dose) IMI, QIV 0,5ml (adult dose) IMI	1 or 2 doses[†]

*Note: influenza vaccine is not recommended for infants <6 months of age. †2 doses should be administered ≥ 1 month apart during 1st year of vaccination, thereafter one dose. If QIV was administered as the first dose and is not available for the second dose, then TIV can be given.

7.1.8 Influenza and COVID-19 vaccination

In October 2021, the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recommended that co-administration of influenza and COVID-19 vaccines is acceptable to maximize uptake of both vaccines, especially among those at high risk of severe influenza illness or COVID-19 [50]. A recommendation is to use contralateral limb for injection of COVID-19 vaccine, when delivered during the same visit [3]. In South Africa, currently there are no COVID-19 vaccines available. However, it is recommend to give both vaccines during the same visit when an eligible patient presents to the health facility and both vaccines are available.

7.2 Co-administration of influenza vaccine and childhood vaccinations in the expanded programme of immunization(EPI)

Whilst there is no contraindication to co-administration of influenza vaccine with the vaccines in the EPI programme, the South African EPI programme recommends separating the administration of measles and influenza vaccine by at least 14 days giving the measles vaccine first followed by the influenza vaccine at a later stage/visit. This is to assist with assigning the cause of the adverse event in the event that there is one.

7.3 Chemoprophylaxis of influenza

Annual influenza vaccination is the best way to prevent influenza, because vaccination can be given well before influenza virus exposures occur, and can provide safe and effective immunity throughout the influenza season. Antiviral chemoprophylaxis is currently NOT recommended. However, WHO guidelines state that individuals at high risk of severe disease who have been exposed to a patient with influenza may benefit from presumptive treatment with a full twice-daily 5-day course of antivirals (oseltamivir), even if they do not show signs and symptoms of infection. Alternatively, such patients can be monitored closely for early signs of possible influenza infection, and given antiviral treatment if they occur. [51]

7.4 To prevent transmission of influenza to others, patients should:

- Stay at home until symptoms have resolved (at least 24 hours after fever has defervesced)

- Avoid close contact with others especially those at high risk for severe influenza (see section 5.2.1 for individuals at risk of severe influenza)
- Avoid close contact such as kissing or sharing drinks
- Cover coughs and sneezes (cover mouth and nose with tissue or cough or sneeze into an elbow)
- Wear a tight fitting mask especially in public places
- Wash hands with soap and water or disinfect with an alcohol-based hand rub regularly
- Limit the number of visitors
- Wipe down surfaces that are frequently touched or shared (doorknobs, remote controls) with a standard household disinfectant

8. Infection prevention and control (IPC) considerations

Human-to-human transmission of influenza viruses occurs either directly or indirectly through close, unprotected contact with large respiratory droplets. The role of smaller droplet nuclei at close-range exposure in transmission of influenza is not known, but may be more important in certain settings (e.g. aerosol-generating procedures associated with increased risk of virus transmission). Collection of nasopharyngeal swabs and aspirates is considered as aerosol generating. Any patient with suspected influenza could also have COVID-19, hence appropriate precautions must be taken. Therefore, IPC precautions need to be focused on controlling respiratory droplet spread.
When working in direct contact with patients, Standard and Droplet Precautions should be applied. Recommended IPC precautions when caring for patients with suspected or confirmed influenza include:

- Standard Precautions:
  - Hand hygiene: washing hands with soap and water or the use of an alcohol-based hand rub
  - Use of personal protective equipment (PPE): this includes facial protection (by means of a medical mask and eye-visor/goggles or a face shield) as well as use of a gown and clean gloves
- Droplet Precautions:
  - Wear a medical mask if working within approximately 1 metre of the patient or upon entering the room/cubicle of a patient on Droplet Precautions
  - Perform hand hygiene before and after patient contact and immediately on removal of a medical mask

- IPC precautions when performing aerosol-generating procedures associated with an increased risk of infection transmission (e.g. aspiration/open suctioning of the respiratory tract, including for the collection of respiratory tract specimens, intubation, resuscitation, bronchoscopy, autopsy):
    - Wear a particulate respirator (e.g. fit-tested N95 respirator), a clean non-sterile long-sleeved gown, and gloves
    - Perform hand hygiene before and after patient contact and after PPE removal
- IPC precautions for patients who are mechanically ventilated or undergoing respiratory therapy:
    - Mechanically ventilated patients: Standard and Droplet Precautions (but when aerosol-generating procedures are performed, particulate respirators need to be worn)
    - Chest physiotherapy: Standard and Droplet Precautions. A medical mask should be worn by the patient if possible
- Nebulisation: Standard and Droplet Precautions.

9. Public Health Response to Influenza

Influenza epidemics occur each year during the winter season. Vaccination of high-risk groups and individuals wishing to protect themselves against influenza is recommended prior to the expected start of the annual influenza season. No public health response is required in response to isolated cases of influenza or outbreaks of mild disease especially in the influenza season.

9.1 Outbreaks should be investigated in the following circumstances:

- A cluster of two or more cases of severe respiratory illness (requiring hospitalisation)
- An outbreak in a closed community e.g. care home, school, healthcare facility, where individuals in the community are at substantial increased risk of severe disease, or the outbreak is causing substantial disruption.

9.1.1 During an outbreak in a closed or semi-closed community the following measures should be considered:

- Isolation of residents of closed settings for the duration of the infectious period (five days after symptom onset).
- Cohorting of patients (that is, in separate hospital bays or on separate floors of a residential home, dormitories) may be necessary.

- Residential homes may need to be closed to new admissions until the outbreak is controlled.
- Care must be taken when discharging a patient from a ward with a known influenza outbreak to a care home, or vice versa.
- Full or partial school closures are not generally recommended on public health grounds, although it is recognized that they may be considered on logistical grounds by the school.
- Administer the current season's influenza vaccine to unvaccinated residents and health care personnel. It is important to note though that because influenza spreads fast it is possible that it will be widespread by the time an outbreak is identified and therefore vaccination may not be effective.

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