influenza pandemic and other public health emergencies.

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Influenza

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

Version 1.3

Summary of changes:

Date reviewed	Reviewed by	Summary of changes
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

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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. 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- Page6

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.

Influenza vaccination is strongly recommended as co-circulation with SARS-CoV-2 is very likely. Preventing severe influenza will decrease the burden on the health care system.

Risk groups for severe/complicated influenza disease - Page 6-7

- Pregnant women (including the post-partum period)
- HIV–infected individuals
- 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)

Groups targeted for Department of Health 2020 influenza vaccination campaign - Page 13, in order of priority. This applies to public and privately funded vaccine.

- It is mandatory for all health care workers to be vaccinated
- Individuals age >65 years
- Individuals with cardiovascular disease (including chronic heart disease, hypertension, stroke and diabetes) and chronic lung disease (including asthma and chronic obstructive pulmonary disease)
- Pregnant women
- People living with HIV and AIDS

Recommended inactivated influenza vaccine (IIV) formulation for 2020 - Page 12

- an A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- an A/South Australia/34/2019 (H3N2)-like virus;
- a B/Washington/02/2019-like (B/Victoria lineage) virus; and
- a B/Phuket/3073/2013-like (B/Yamagata lineage) virus*

*the quadrivalent vaccine is only available in the private sector.

Treatment of influenza - Page 9-11

Neuraminidase inhibitors (oseltamivir or zanamivir) 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.

Dosage of influenza vaccine - Page 14

- Adults 0.5ml IMI single dose
- 3 years - 8 years – 0.5ml IMI 1 or 2 doses*
- 6 months-2 years-0.25ml IMI 1 or 2 doses*

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

Additional questions from health professionals can be directed to: National Institute for Communicable Diseases (NICD) **Hot line: +27 82 883 9920;** for Laboratory support: NICD, Centre for Respiratory Diseases and Meningitis: **011 386 6390/ 011 386 6392**

1. Introduction

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 categorized into subtypes. 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 into strains based upon antigenic properties. Humoral immunity to influenza viruses is generally thought to be strain-specific and acquired through infection or vaccination. Seasonal influenza epidemics can be caused by new virus strains that are antigenically distinct from previously circulating virus strains to which a population has 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. 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).

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 African hospitals, 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. In South Africa, it is estimated that approximately 11 800 seasonal influenza-associated deaths occur annually[8]. In addition an estimated 47 000 episodes of influenza-associated severe acute respiratory illness occur annually of which 22 481 result in hospitalization [9]. Approximately 5% of these deaths are in

children aged <5 years. Among individuals aged ≥5 years, an estimated 50% of influenza-associated deaths are in the elderly and approximately 30% are in HIV-infected individuals [1,9]. 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 in recent years, the majority (~90%) occurred in HIV-infected individuals 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. [11]

The highest rates of influenza-associated hospitalisation are in those aged ≥65 years, HIV-infected individuals and children <5 years (in particular children < 1 year). [1, 9, 10, 12, 13]. Recent 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 mine (aOR, 13.8) were significantly associated with increased risk of influenza associated hospitalization [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).
In tropical areas, influenza occurs throughout the year. In temperate areas, influenza is highly seasonal and typically occurs during winter months like in South Africa.

3. 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 hemagglutinin subtypes (H1, H2 and H3) and two neuraminidase subtypes (N1 and N2) have circulated stably in the human population and are responsible for annual epidemics.

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

4. 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, 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 [17]. Children have the highest rates of seasonal influenza infection and illness in this group can amplify viral transmission in the community.

5. Clinical presentation and risk factors for influenza

Infection with influenza viruses can give rise to 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, myocarditis, transverse myelitis, pericarditis and Reye syndrome. For purposes of clinical management, influenza disease can be categorised as follows [18]:

- **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.

5.1 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, 10, 11, 15, 16, 19, 20] a recent study from South Africa has 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-hospitalization[14]. In addition HIV-infected individuals with severe immunosuppression compared to those with mild immunosuppression had three times increased odds of influenza associated hospitalization [14].

Risk groups for severe/complicated influenza disease include:

- Pregnant women (including the post-partum period)
- HIV–infected individuals[14, 21]
- Individuals with tuberculosis[15, 16, 22]
- Persons of any age with chronic disease, including:
    - Pulmonary diseases (e.g. asthma, COPD)[23]
    - Immunosuppression (e.g. persons on immunosuppressive medication, malignancy)
    - Cardiac diseases (e.g. congestive cardiac failure), except for hypertension[23]
    - Metabolic disorders (e.g. diabetes mellitus)[24]
    - 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 ≤18 years receiving chronic aspirin therapy
- Persons who are morbidly obese (i.e. BMI ≥40)[25]
- Young children (particularly <2 years of age)

6. 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, pneumonia surveillance programme), and testing should continue as guided by those individual surveillance programmes.

6.1 Laboratory testing for influenza

The NICD no longer offers routine diagnostic testing, including for influenza, outside of established surveillance programmes at specific sites. Diagnostic capacity to test for influenza viruses has now been established in various National Health Laboratory services (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 – 082 883 9920** before samples are collected.

In line with WHO recommendations, molecular diagnostics (real-time multiplex PCR for influenza A and B virus or Gene expert 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 and should not preclude starting empiric antiviral treatment where sound indications exist.

Sandringham, 2131. Please complete specimen submission form: http://www.nicd.ac.za/wp-content/uploads/2019/03/CRDM-specimen-submission-form-v1_28-Feb-2019.pdf

7. Clinical management and considerations for treatment of influenza

Influenza is detectable in approximately 7% of children aged < 5yrs hospitalised with pneumonia and 9% of individuals aged ≥5 years hospitalized with pneumonia in South Africa. [28, 29]. During the influenza season this increases to approximately 20-40% of all people 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 and consideration must be given to including oseltamivir as part of empiric treatment where indicated (see section 5.1) 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.

7.1 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 hospitalized 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 5.1).

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 [30-32] . Because of the large sample sizes required, there have not been RCTs conducted specifically to evaluate the effect of oseltamivir against severe outcomes