

# Influenza...

## Circulating viruses and vaccination

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### Abstract

Influenza or “flu” is an acute viral respiratory infection caused by seasonal influenza viruses and distinct outbreaks of varying degrees occur every year. The severity of illness depends on the characteristics of both the infected person and the virus. Circulating seasonal influenza viruses have the ability to change constantly. In order to ensure optimal efficacy, the vaccine strains selected should match the circulating strains as closely as possible. Annual influenza vaccination is the most effective method to prevent flu and complications from flu. It is especially important to vaccinate persons at increased risk for severe disease or influenza-related complications.

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### Introduction

Influenza, also known as “flu”, is an acute viral infection of the respiratory tract caused by influenza viruses, most commonly influenza A and B viruses.<sup>1-4</sup> In temperate climates, seasonal epidemics occur nearly every year, mainly during the winter season.<sup>4,5</sup>

Flu is usually a self-limiting illness and most people recover within a few days.<sup>3,4</sup> However, flu can also cause severe illness, which can result in serious complications, hospitalisation or death.<sup>1,3</sup> It has been estimated that around 11 800 seasonal influenza-related deaths occur every year in South Africa.<sup>1</sup>

The influenza viruses have the ability to undergo constant changes and, to ensure optimal vaccine efficacy, the vaccine strains selected should match the circulating strains as closely as possible.<sup>1,4</sup>

This article will focus on the circulating influenza A and influenza B viruses, virus strains included in the vaccine as well as recommendations regarding the use of the flu vaccine. Annual flu vaccination is still the most effective method to prevent flu and complications from flu.<sup>1,2,6</sup>

### What is influenza?

Flu is a highly infectious viral disease and the virus is spread from one person to another via infectious droplets expelled by coughing or sneezing.<sup>1,2</sup> The virus can also be spread by touching contaminated surfaces, objects or hands and then touching the eyes, nose or mouth.<sup>1-3,7</sup>

The incubation period is typically two days (varies from one to four days).<sup>1,2</sup> The severity of illness depends on the characteristics of both the infected person and the virus. Clinical presentation can vary from asymptomatic infection to severe illness with complications, which can be life-threatening.<sup>1-3,7</sup>

### Flu symptoms

Characteristic symptoms include a sudden onset of fever, chills, myalgia (the back muscles are mostly affected), headache and extreme fatigue.<sup>2,3</sup> Other symptoms include a dry or non-productive cough, sore throat, a stuffy or runny nose<sup>2,3</sup> and sometimes gastrointestinal symptoms (more common in children).<sup>1,7</sup>

Flu is generally a self-limiting illness. Most people will feel better after three to seven days and recover without sequelae.<sup>1-3,8</sup> However, malaise and cough may persist for more than two weeks.<sup>1</sup>

### Complications associated with flu

Flu-related complications include secondary bacterial or viral infection including pneumonia, sinusitis and otitis media.<sup>1-3</sup> Pneumonia (most commonly secondary bacterial pneumonia) or lower respiratory tract infections are the most common flu-related complications.<sup>1,2</sup> Flu infections may also trigger exacerbations of chronic illnesses.<sup>1</sup> Other complications (rarely) include multi-organ failure, encephalopathy, myocarditis (inflammation of the heart), transverse myelitis (inflammation of the spinal cord), pericarditis and Reye's syndrome.<sup>1,2,3</sup>

**Table I. Circulating influenza A and B viruses, the severity of illness and age groups commonly affected by influenza A and B viruses<sup>2,11</sup>**

	Influenza A virus	Influenza B virus
Current circulating virus types	<ul style="list-style-type: none"> <li>Influenza A (H1N1)</li> <li>Influenza A (H3N2)</li> </ul>	<ul style="list-style-type: none"> <li>B/Yamagata lineage</li> <li>B/Victoria lineage</li> </ul>
Severity of illness	Causes moderate to severe illness	Causes milder disease than type A
Age group affected	Affects all age groups	Primarily affects children
Infects	Infects humans and other animals	Only affects humans
Notes	Maintained in nature by wild birds, primarily waterfowl	

People at highest risk for developing severe or complicated illness include very young children, older adults, pregnant women, people with chronic medical conditions (heart, lung, kidney or endocrine disease), those who are immunosuppressed, people with HIV infection, people with tuberculosis, those who are morbidly obese and persons ≤ 18 years receiving chronic aspirin therapy.<sup>1,6-10</sup>

### Influenza virus

There are four types of flu viruses namely A, B, C and D. However, only types A, B and C cause disease in humans. Influenza C viruses usually cause mild respiratory illness, are detected less frequently and are not thought to cause epidemics.<sup>2,9,11</sup> The fourth type, influenza D viruses, are not known to cause disease in humans and affect animals, primarily cattle.<sup>11</sup>

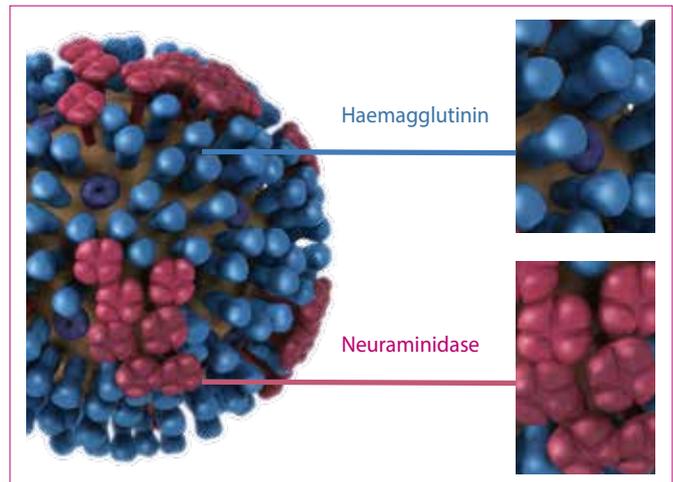
Information regarding circulating influenza A and B viruses, the severity of illness and age groups commonly affected are listed in Table I.<sup>2,11</sup>

### Classification of flu viruses

#### Influenza A viruses

Influenza A virus subtypes are determined by the two surface proteins on the surface of the influenza virus (Figure 1):<sup>1,2,5,9,11,12</sup>

- Haemagglutinin (H)
  - Plays a role in virus attachment to cells
  - There are 18 different subtypes (H1 through H18)
  - Three major subtypes H1, H2 and H3 circulate in humans<sup>1,2,5</sup>
- Neuraminidase (N)
  - Plays a role in virus penetration into cells
  - There are 11 different subtypes (N1 through N11)
  - Two major subtypes N1 and N2 circulate in humans<sup>1,2,5</sup>



**Figure 1.** 3D Graphical representation of the biology and structure of an influenza virus. Haemagglutinin (H) and neuraminidase (N) are two proteins on the surface of the virus.<sup>12</sup>

Adapted from the Centers for Disease Control and Prevention (CDC).<sup>12</sup> Available from: <https://www.cdc.gov/flu/images.htm>

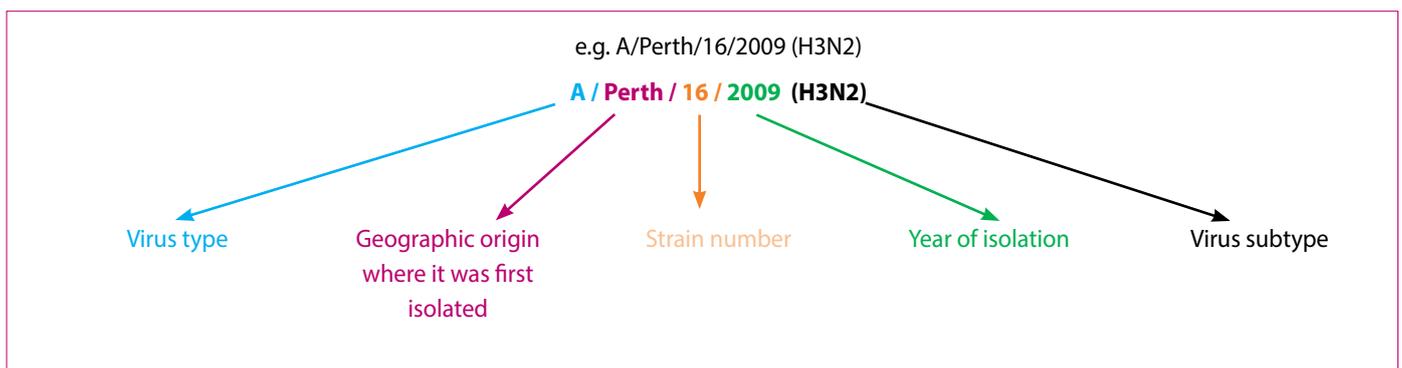
Based on their antigenic properties, the influenza viruses are further classified into strains.<sup>1,11</sup>

#### Influenza B viruses

Influenza B viruses are divided into lineages and strains.<sup>9,11</sup>

#### Nomenclature: Decoding the names of flu viruses

Human influenza viruses are named according to an internationally accepted naming convention for influenza viruses that was accepted by the World Health Organization (WHO) in 1979.<sup>11</sup>



**Figure 2.** Decoding the name of human-origin influenza viruses

The following components are included in the name (Figure 2):<sup>2,11</sup>

- Virus type (e.g. A, B or C)
- The host of origin e.g. swine, equine, etc. (no host of origin is given for human-origin viruses)
- Geographic origin where it was first isolated
- Strain number
- Year of isolation and
- Virus subtype

### Evolving nature of the flu virus

The flu viruses evolve constantly and in unpredictable ways.<sup>1</sup> Influenza viruses may undergo minor or major changes in the two surface proteins.<sup>2</sup>

Minor changes in the surface proteins occur progressively from season to season.<sup>2,5</sup> Minor changes are known as antigenic drifts and are associated with localised outbreaks of variable extent and severity.<sup>5</sup> All three types of influenza viruses (A, B, C) can undergo drifts.<sup>2</sup> Influenza A and B viruses are both responsible for seasonal epidemics.<sup>1,11</sup>

Major changes in one or both of the surface antigens are referred to as antigenic shifts.<sup>5,9</sup> Antigenic shifts may lead to the emergence of a completely new (novel) strain. If the new virus spreads efficiently from person to person, in a population where there is little or no existing immunity, the new strain can give rise to a flu pandemic.<sup>1,2,5,9</sup> Influenza type A viruses are the only type known to have caused pandemics.<sup>9</sup>

### Circulating seasonal flu viruses in South Africa

According to the National Institute for Communicable Diseases (NICD), in South Africa, the 2018 flu season started in the first week of May and was "dominated by influenza A(H1N1)pdm09

until mid-July".<sup>13</sup> Influenza A(H1N1)pdm09 is the same flu virus that caused the 2009 global flu pandemic. It is now part of the seasonal circulating flu strains.<sup>1,13</sup>

Figure 3 illustrates the change in the dominant influenza virus during the 2018 flu season in South Africa as detected by Viral Watch 2018. The findings from the influenza-like illness at primary healthcare clinics and national syndromic surveillance for pneumonia (both are part of the NICD influenza surveillance programmes) have been similar to those of Viral Watch.<sup>13</sup>

### Flu vaccine

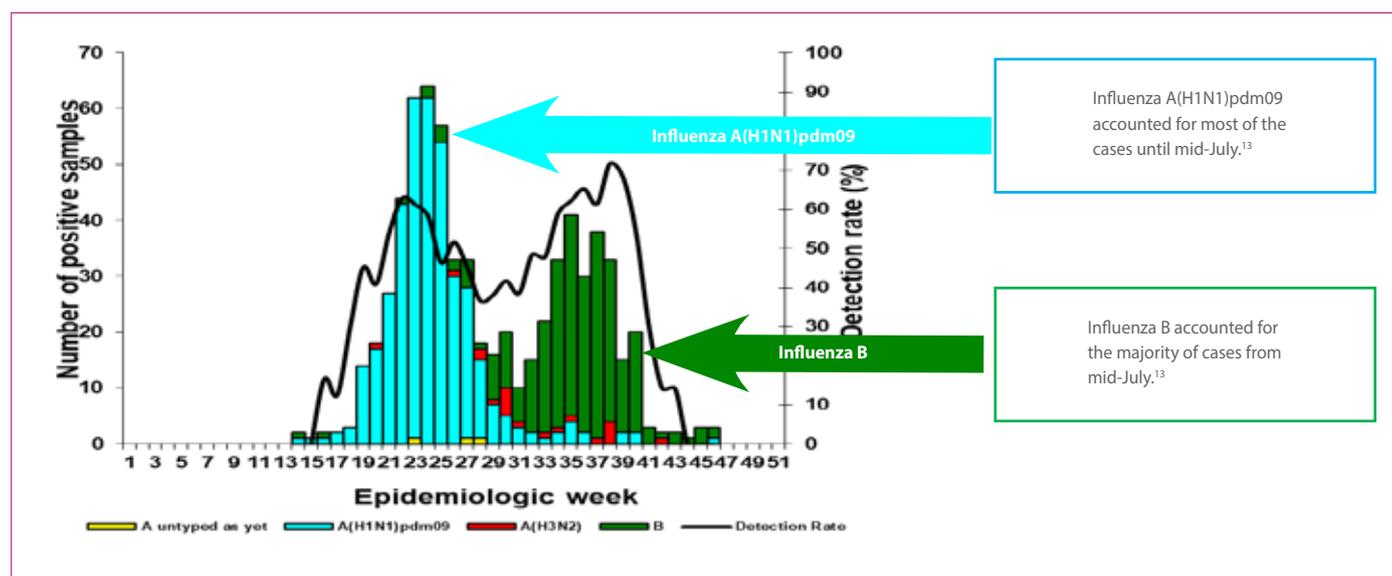
Vaccination is the most effective way to prevent flu.<sup>9</sup> The flu vaccines used in South Africa are inactivated vaccines and are either split or subunit vaccines.<sup>4,14</sup> This means that the flu viruses have been "killed" or inactivated. The vaccines are therefore not infectious and a person cannot get flu from the vaccine.<sup>4,10,14</sup>

It is also important to note that the flu vaccine only provides protection against influenza viruses included in the vaccine and will not afford protection against other circulating viruses, for example against rhinoviruses which cause common colds.<sup>10</sup>

### Strains included in the flu vaccine

The flu vaccine only provides protection against the different strains of influenza viruses included in the vaccine. It is therefore important that the vaccine strains match the circulating strains in the environment as closely as possible.<sup>9,10</sup>

The World Health Organization Global Influenza Surveillance and Response System (GISRS) continuously monitors the influenza viruses circulating in humans and updates the recommendations about the strains to be included in the flu vaccine for the forthcoming winter. This is done twice a year; in February for



**Figure 3.** Viral Watch 2018: Number of positive samples by influenza types and subtypes and detection rate\*

\* Only reported for weeks with >10 specimens submitted.

Patients known to have acquired influenza abroad or from contact with travellers are not included in the epidemiological curve.<sup>13</sup> (Adapted from NICD Communicable Disease Communiqué, Nov 2018, Available from: <http://www.nicd.ac.za/wp-content/uploads/2018/11/Influenza.pdf>)

the northern hemisphere and in September for the southern hemisphere.<sup>9,15</sup>

The following strains have been recommended for the 2019 southern hemisphere trivalent influenza vaccines:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus<sup>15</sup>
- an A/Switzerland/8060/2017 (H3N2)-like virus<sup>15</sup>
- a B/Colorado/06/2017-like virus<sup>15</sup>

If a quadrivalent influenza vaccine becomes available in South Africa, it should contain the abovementioned strains as well as:

- a B/Phuket/3073/2013-like virus.<sup>15</sup>

### **Who should be vaccinated?**

Some flu vaccines can be given from six months of age while other flu vaccines are registered from older ages. Please refer to individual package inserts for information regarding age restrictions.<sup>8</sup>

The flu vaccine is recommended for everyone who wishes to protect himself or herself against flu, but especially for people at high risk of flu and its complications.<sup>1</sup>

Risk groups include:<sup>1,3,7-9</sup>

- Pregnant women at all stages of pregnancy, including the postpartum period
- Children aged six months to 59 months
- Elderly people (over 65 years of age)
- Individuals over six months of age with chronic conditions such as chronic respiratory disease (including tuberculosis), chronic heart diseases, chronic kidney diseases, diabetes mellitus and similar metabolic disorders (inherited metabolic disorders and mitochondrial disorders), chronic liver disease or chronic neurological disease
- People who are immunosuppressed due to any cause (including HIV-infection and immunosuppression caused by medications or disease)
- Individuals aged six months to  $\leq 18$  years on long-term aspirin therapy (owing to the possible risk for experiencing Reye's syndrome if they develop flu)
- People who are morbidly obese (body mass index  $\geq 40$  kg/m<sup>2</sup>)
- Residents of old-age homes, rehabilitation and chronic care institutions

The flu vaccine is also recommended for healthcare workers and for household contacts of persons at high risk of severe flu or flu-related complications. In addition to being protected themselves, vaccination also helps to reduce the spread of the influenza virus. This contributes to the protection of those who may have a suboptimal response to their own vaccination or who cannot be vaccinated.<sup>1-3,8,16</sup>

Flu vaccines, overall, are most effective when administered to healthy adults and children two years of age and older.<sup>1</sup> However,

even though certain groups (such as immunocompromised people, the elderly and infants), may not mount a good enough response to the vaccine, the vaccine may still reduce the incidence of severe disease, bronchopneumonia, hospital admission and mortality.<sup>1</sup>

### **When should the vaccine be given?**

To ensure optimal protection, it is best to vaccinate before the flu season starts.<sup>16</sup> Once the vaccine is given, it takes about 10–14 days to develop a protective immune response.<sup>7,16</sup>

In South Africa, the flu season typically starts around May and the optimal time to vaccinate is around March/April.<sup>7</sup> However, it is never too late in the season to vaccinate; the flu vaccine can still be beneficial and will provide protection for the remainder of the flu season.<sup>7,16</sup>

### **How many doses should be given?**

Children aged six months through eight years who are being vaccinated against flu for the first time should receive two age-appropriate doses of the flu vaccine. The second dose should be administered at least 28 days after the first dose. The immune system is "primed" with the first dose and the second dose provides immune protection.<sup>1,10,16</sup> Thereafter, only one dose of the flu vaccine is required in subsequent seasons.<sup>1,8</sup>

Only one dose of the flu vaccine is recommended each season for adults and children nine years of age and older. Studies have not shown any benefit when more than one dose of flu vaccine was administered to adult patients during the same flu season.<sup>1,10,16</sup>

### **Why should the flu vaccine be given every year?**

The immune response produced by the vaccine wanes over time and in order to ensure optimal protection against flu, revaccination is recommended every year. In addition, the current flu vaccine (based on the current circulating flu viruses) may differ from the flu vaccine used in the previous season.<sup>9,10</sup>

### **Can the flu vaccine be used during pregnancy?**

Pregnant women (and women up to two weeks postpartum) are more prone to severe illness from flu and have a higher risk of hospitalisation for flu-related complications compared to non-pregnant women.<sup>1,17</sup> This may be related to changes to the immune system, lungs and heart during pregnancy.<sup>17</sup>

Flu during pregnancy may also be harmful for the developing baby. Risks associated with flu during pregnancy include prematurity, lower birth weight and perinatal mortality.<sup>3,17</sup>

The flu vaccine has been found to be effective and well-tolerated during pregnancy. It can be given during any trimester of pregnancy, as well as the postpartum period.<sup>1,2,3</sup> The flu vaccine given during pregnancy does not only protect the mother against flu, it also offers secondary protection to infants during the first months after birth, when they are too young to be vaccinated.<sup>1,3,17,18</sup>

A retrospective study by Thompson MG *et al.*, 2018, showed that the flu vaccine reduced a pregnant woman's risk for being hospitalised with flu by an average of 40 percent, which further strengthens the rationale for influenza vaccination programmes for pregnant women.<sup>17,18</sup>

### What are the safety concerns with the flu vaccine?

#### Contraindications

The flu vaccine is contraindicated in persons with a history of a severe, life-threatening (anaphylactic) allergy to the vaccine or any ingredient in the vaccine.<sup>1</sup>

Most of the flu vaccines are prepared from viruses grown in embryonated hens' eggs. As a result, egg allergy has been considered a contraindication to the flu vaccine. However, the recommendations regarding the use of the flu vaccine in persons with egg allergy have been revised. According to the new guidelines, persons with a mild egg allergy (whose allergy involves only urticaria or hives) may receive the flu vaccine.<sup>1,8,19</sup> As a precaution, vaccination of individuals who had an anaphylactic reaction (or reaction more severe than hives) to eggs, should be performed in a controlled environment or medical setting where they will be able to recognise and manage severe allergic conditions.<sup>8,19</sup>

#### Special precautions

Although persons with minor illnesses without fever may be vaccinated, it is best to postpone vaccination in persons with a moderate or severe acute illness, with or without fever.<sup>1,2,3</sup> This will allow for differential diagnosis and prevent attributing signs and symptoms due to acute illness incorrectly to vaccination.<sup>3</sup>

A history of Guillain-Barré syndrome within six weeks following a previous flu vaccine is a precaution for future vaccination.<sup>1,2</sup>

#### Side-effects

The most common side-effects reported with the use of the flu vaccine include injection site reactions such as pain, swelling or redness.<sup>2,3</sup> Nonspecific systemic symptoms include low grade fever, headache, fatigue, malaise, myalgia and arthralgia.<sup>3</sup> Side-effects usually last about one or two days and improve without treatment.<sup>3</sup>

Systemic side-effects from the flu vaccine (such as mild fever and body aches) may be confused with flu symptoms and people may wrongly perceive that the flu vaccine gave them flu.<sup>10</sup>

Please refer to the individual package inserts for a detailed list of ingredients, contraindications, precautions and side-effects.

### Conclusion

Annual flu vaccination is one of the most effective methods to prevent flu and complications from flu.<sup>1,6</sup> For the flu vaccine to be effective, it is important that the vaccine strains match the circulating strains in the environment as closely as possible.<sup>9,15</sup>

The flu vaccines can be given from six months of age (depending on product) and are recommended for everyone, but especially for people at highest risk of developing flu complications.<sup>1,6,9</sup>

In addition, to help prevent the spread of flu, patients should be advised to:<sup>1,7,9</sup>

- Practice good respiratory hygiene – cover their mouth and nose with a tissue when coughing or sneezing and dispose of the tissue correctly; if a tissue is not readily available people should be taught to sneeze into their sleeve or elbow
- Wash their hands regularly with soap and water or use alcohol-based hand sanitiser<sup>9</sup>
- Avoid contact with sick people
- Avoid touching their eyes, nose or mouth
- Use household disinfectant to wipe down surfaces that are frequently touched
- Rather stay at home and avoid or limit contact with other people if they are sick

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