Vaccination against influenza saves lives – a 2021 update

JC Meyer,[1,2] M Sibanda,[1,2] RJ Burnett[2,3]

[1] School of Pharmacy, Sefako Makgatho Health Sciences University, South Africa

[2] South African Vaccination and Immunisation Centre, Sefako Makgatho Health Sciences University, South Africa

[3] Department of Virology, School of Medicine, Sefako Makgatho Health Sciences University, South Africa

Corresponding author, email: hannelie.meyer@smu.ac.za

Abstract

Influenza is a highly contagious, acute respiratory viral infection responsible for annual epidemics causing severe morbidity and mortality. Vaccination remains the most effective, live-saving preventative strategy, especially amongst populations at high risk of developing influenza-related complications. The inactivated trivalent seasonal influenza vaccine contains two World Health Organization (WHO)-recommended influenza A and one influenza B strains, while the quadrivalent vaccine contains an additional B strain, providing broader protection against co-circulating influenza B lineages. Healthcare workers are instrumental in ensuring effective communication about the benefits of influenza vaccination to achieve optimal seasonal influenza vaccination coverage. This article provides an updated overview of the influenza vaccines with special consideration of the current COVID-19 pandemic.

Keywords: influenza, vaccination, immunisation, prevention

Republished from: *Prof Nurs Today* 2021;25(1):16-20

S Afr Pharm J 2021;88(2):13-18

Introduction

Influenza, a viral infection often perceived as a mild illness, is a highly communicable disease associated with severe morbidity and mortality.[1-3] Annually, influenza is responsible for an estimated one billion cases with up to 650 000 influenza-related respiratory deaths worldwide.[3,4] Being one of the greatest public health challenges globally, the World Health Organization (WHO) recommends annual vaccination as the most effective way to protect against influenza.[3]

South African burden of influenza

In South Africa, severe illness caused by influenza affects over 45 000 people annually, with almost 50% of them requiring hospitalisation.[1,2] The highest rates of hospitalisation are in the elderly (≥ 65 years), people who have chronic illnesses like diabetes, lung disease and heart disease, and children < 5 years old.[2,5] Pregnant women, people with tuberculosis and the immunocompromised are at increased risk of hospitalisation and death from influenza.[2,5] Influenza-related deaths are estimated at more than 11 000 annually,[6,7] with approximately 50% occurring in the elderly and 30% in people infected with HIV.[8] Pneumonia is a leading cause of mortality and morbidity, with approximately 14% of South African patients hospitalised for pneumonia and 25% of patients with influenza-like illness (fever and cough) testing positive for influenza.[2,5] In 2020, influenza activity in South Africa was lower than expected due to widespread use of non-pharmaceutical interventions such as social distancing, mask-wearing, sanitising and lockdown measures, enforced to curb the transmission of SARS-CoV-2 .[9,10]

Viruses responsible for seasonal and pandemic influenza

Influenza viruses belong to the *Orthomyxoviridae* family. They are single-stranded RNA viruses, whose segmented genomes and error-prone replication process respectively, allow for gene exchange/gene reassortment (antigenic shift), and mutations (antigenic drift), which determine their virulence and circulation.[2] Of the three types of human influenza viruses (A, B and C), two (influenza A, infecting several species, and influenza B, infecting mainly humans) cause seasonal epidemics, while influenza A also causes global pandemics.[1,2,11] Influenza A viruses are divided into subtypes based on two surface glycoproteins, namely haemagglutinin (H1 to H18) and neuraminidase (N1 to N11). Annual human epidemics are caused by subtype combinations involving H1, H2, H3, N1 and N2.[2] Influenza A (H3N2) and influenza A (H1N1) are currently the major subtypes causing seasonal influenza.[11,12]

Influenza B viruses are classified into lineages, namely as B/Yamagata or B/Victoria lineages.[11,13] Unlike influenza A which infects other mammalian and avian species, influenza B infects only humans and seals.[12] This limited host range makes interspecies gene reassortment unlikely, thus influenza pandemics are not caused by influenza B.[12]

Transmission of influenza

Influenza viruses are spread from person-to-person through respiratory droplets.[14] These can be spread up to approximately 1.8 metres via coughing, sneezing or talking, with inhalation

through the nose or mouth.[2,14,15] Droplets can also contaminate the hands or other surfaces which may be touched, with the virus subsequently deposited into the mouth, nose and eyes.[2,14,15]

The average incubation period for influenza is two days, with the first three to four days after symptoms start being most contagious.[2,15] The virus can also be shed from a few days before the person presents with any symptoms, up to five to seven days after the onset of illness.[2,15] Very young children, severely affected adults and immunocompromised patients can, however, be infectious for > 10 days after the onset of illness.[2,15] Asymptomatic infected people can also transmit influenza.[15]

Symptoms and clinical presentation of influenza

Mild uncomplicated influenza presents with sudden onset of respiratory symptoms (cough, pharyngitis, rhinitis/coryza) and systemic symptoms (fever, malaise, headache, myalgia, arthralgia).[2,16] Gastrointestinal (vomiting, diarrhoea) symptoms may present, but more commonly in children.[2,16] Most cases will recover within a week, while some cases will develop complicated or severe influenza, which requires hospitalisation and may result in death.[2,16]

Influenza vs common cold

Both the common cold and influenza are respiratory illnesses but caused by different viruses.[16,17] It is often difficult to differentiate between a cold and influenza as they share many signs and symptoms.[16,17] Laboratory tests are available to test for influenza, provided testing is done within the first few days of illness. This is not routinely recommended for uncomplicated illness, except in sentinel surveillance sites.[2,13,16,17]

Influenza symptoms are usually much worse than those of the common cold, which generally does not result in severe complications such as bacterial infections, pneumonia or hospitalisation.[16,17] Box I illustrates the main differences in signs and symptoms for the common cold and influenza.[17]

Prevention of influenza

Influenza surveillance

Influenza surveillance plays an important public health role in influenza prevention and control, informing timely interventions

Box I: Differences in signs and symptoms for the common cold and flu[17]

Signs and symptoms	Common cold	Influenza
Symptom onset	Gradual	Abrupt
Fever	Rare	Usual
Aches	Slight	Usual
Chills	Uncommon	Fairly common
Fatigue, weakness	Sometimes	Usual
Sneezing	Common	Sometimes
Chest discomfort, cough	Mild to moderate	Common
Stuffy nose	Common	Sometimes
Sore throat	Common	Sometimes
Headache	Rare	Common

STEP 1: Get vaccinated

- Annual influenza vaccination is the most effective method to prevent influenza
- People who are at high risk of developing complications from influenza must be vaccinated:
  # Pregnant women (any stage of pregnancy) # People with chronic medical conditions # Children aged 6 months – 5 years # Adults aged ≥ 65 years # Healthcare workers
- Important: The influenza vaccine cannot cause influenza; it does not contain any live virus
- A slight fever and body aches after vaccination are normal; this will subside within 2 days

STEP 2: Wash hands frequently

- Keep your hands clean to protect yourself and your family against influenza and other infections
- Wash hands properly:[21] Wet with clean running water → Use enough soap → Rub palm to palm → Rub back of hands → Rub in-between fingers → Interlock fingers (fingers pressed to opposing palms) and rotate → Rub thumbs → Rotational rubbing with clasped fingers in palm of opposite hand → Rinse well with water → Dry with single use towel OR by shaking in the air
- Remember: Proper handwashing takes as long as singing "Happy Birthday" twice
- Use an alcohol-based hand rub if soap and water are not available

STEP 3: Avoid touching the eyes, nose and mouth

- Influenza viruses spread through droplets
- Droplets enter the body through the eyes, or when inhaled through the nose and mouth
- Droplets on other surfaces, when touched, can contaminate the hands
- Do not touch your face – keep hands away at all times
- Use a clean tissue, if you need to touch your eyes, nose or mouth OR wash your hands first

STEP 4: Avoid being around sick people

- Influenza is very contagious and spreads easily from person to person
- Droplets containing the virus can spread up to 1.8 m and be inhaled
- Avoid crowded spaces, e.g. public transport, schools, sports events, nursing homes where there is a greater risk of being exposed to infected people

STEP 5: If you don't feel well, stay at home

- If you don't feel well, and suspect you might be sick, you expose those around you to the same infection → Stay at home to prevent spreading influenza or other infections
- Avoid contact with high-risk groups to save their lives
- Cover nose and mouth when coughing/sneezing (e.g. cough into a tissue, cough into a sleeve)
- Immediately discard any used tissues
- Frequently wash hands with soap and water OR disinfect with an alcohol-based hand rub
- Wipe down all surfaces that are frequently touched or shared (doorknobs, remote controls) with a standard household disinfectant
- Limit the number of visitors
- Stay at home for at least 24 hours after fever (temperature > 37.8 °C) has subsided without the use of an antipyretic

STEP 6: If you are ill isolate yourself

- Being ill with influenza, puts others around you at risk
- Prevent spreading the influenza virus by immediately isolating yourself
- Follow precautionary measures as in Step 5
- Stay at home for at least 24 hours after fever (temperature > 37.8 °C) has subsided without the use of an antipyretic

Figure 1: Steps to protect against influenza and to prevent transmission of the virus[2,13,16,20,21]

and appropriate resource allocation.[13] The WHO Global Influenza Surveillance and Response System provides essential information on the current circulating virus strains, to support the selection of influenza strains for the following season's vaccine production, with separate recommendations for the southern and northern hemispheres.[13,16,18]

Risk factors and protection against influenza

Although influenza can result in severe illness in previously healthy people, high-risk groups can develop severe illness with subsequent hospitalisation.[19] Figure 1 illustrates how to protect individuals and communities against acquiring and transmitting influenza. Note that the **first step** recommended by WHO is to get **vaccinated**.[2,13,16,20,21]

Influenza vaccines

Influenza viruses mainly circulate during the winter months in South Africa. However, the influenza season could start as early as April or as late as July and may persist up to September.[22] Following WHO recommendations for particular strains to be included, influenza vaccines are usually available from March.[2] The vaccine is a split-virion inactivated influenza vaccine (IIV), with recommended strains grown in embryonated eggs.[23-25] For the 2021 influenza season both an inactivated trivalent influenza vaccine (TIV) which contains two influenza A and one influenza B strains, and an inactivated quadrivalent influenza vaccine (QIV), containing an additional lineage of influenza B, will be available in South Africa.[23-26] Based on recommendations for the southern hemisphere, the TIV (Influvac®) for use in the 2021 influenza season in South Africa contains the following strains:[18,23]

- A/Victoria/2570/2019 (H1N1)pdm09-like virus
- A/Hong Kong/2671/2019 (H3N2)-like virus
- B/Washington/02/2019 (B/Victoria lineage)-like virus

The QIV (Vaxigrip Tetra®, Influvac Tetra®, Fluarix Tetra®) contains the above strains and an additional lineage of influenza B:[18,24-26]

- B/Phuket/3073/2013-like (B/Yamagata lineage) virus

The additional B strain provides broader protection against co-circulating influenza B lineages, hence has the potential to further reduce influenza-related morbidity and mortality.[27] Evidence has also shown efficacy, safety and immunogenicity of the QIV in children (3–35 months).[28] Although influenza A infection is more common than influenza B, the clinical severity and the risk of hospitalisation in children were found to be similar.[29] Hence, the QIV could provide more optimal protection against severe influenza in children.[29]

Influenza vaccination target groups

The most effective method currently available to prevent and protect against influenza is vaccination.[2,3] Ideally everybody aged > 6 months should receive annual influenza vaccination for the benefit of herd immunity.[7,30,31] During a pandemic such as the current SARS-CoV-2, there is a high possibility of co-circulation of viruses.[2] Vaccination against influenza is therefore particularly important to prevent severe influenza.[2] Vaccination during the ongoing COVID-19 pandemic is also important to reduce symptoms that could be confused with those of COVID-19 and to minimise stress on the health system.[32] Although the influenza vaccine does not protect against COVID-19, there is evidence that influenza vaccination lowers COVID-19 hospitalisation and deaths in individuals who are co-infected with COVID-19 and influenza.[32,33] Individuals who are at higher risk of serious influenza complications due to weakened immune responses, and their family contacts, should be prioritised for vaccination (Table I).[2]

Table I: Influenza vaccination recommendations for high-risk groups[2,16,19,34-38]

High-risk group	Comments
Healthcare workers#	Free vaccination was provided in 2020 for the protection of healthcare workers themselves, their patients and vulnerable colleagues to reduce the additional burden on the health system caused by COVID-19. It is expected that this will again be the case for 2021.
Elderly persons#*	Adults aged ≥ 65 years.
Cardiovascular disease and chronic lung disease#*	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#*	At any stage of pregnancy (including 2 weeks after delivery). Vaccination of pregnant women is safe and provides protection to infants for the first few months of life.[36]
HIV-infected#*	People living with HIV and AIDS.[8,19]
Other immunocompromised persons*	Immunocompromised persons include those on immunosuppressive therapies and those with immune disorders.
Persons aged ≥ 6 months with underlying medical conditions, including confirmed pulmonary tuberculosis*	In addition to cardiovascular disease and chronic lung disease mentioned above, individuals (adults/children aged ≥ 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 such as tuberculosis,[37] chronic renal diseases, metabolic disorders (inherited metabolic disorders and mitochondrial disorders), hepatic disease, neurological and neurodevelopmental conditions and haemoglobinopathies (e.g. sickle cell disease).
Persons on long-term aspirin treatment	Persons aged 6 months to ≤ 18 years on long-term aspirin therapy.
Young children	Especially those aged 6 months to 5 years.
Persons who are morbidly obese	Persons with a BMI ≥ 40.[38]
Residents at institutions	Residents of old-age homes, chronic care facilities and rehabilitation institutions.
Family contacts of high-risk individuals	Adults and children who are family contacts of high-risk individuals.

Targeted for the NDoH 2020 influenza vaccination campaign; * Prioritised by the National Department of Health

Table II: Recommended dosage and dosage administration for IIV[2,23-26,34]

Age group	Vaccine	Dose	Number of doses per annum
Children 6 months – 3 years	Trivalent IIV e.g. Influvac® Quadrivalent IIV e.g. Vaxigrip Tetra® Fluarix Tetra®	Consult package insert 0.25 ml or 0.5 ml depending on age 0.5 ml	First year of vaccination: Two doses administered ≥ 4 weeks apart Subsequent seasons: Single dose
Children 3 years – < 9 years	Trivalent IIV e.g. Influvac® Quadrivalent IIV e.g. Vaxigrip Tetra® Influvac Tetra® Fluarix Tetra®	0.5 ml	First year of vaccination: Two doses administered ≥ 4 weeks apart Subsequent seasons: Single dose
Adults and children ≥ 9 years	Trivalent IIV e.g. Influvac® Quadrivalent IIV e.g. Vaxigrip Tetra® Influvac Tetra® Fluarix Tetra®	0.5 ml	Single dose
Age group	**Route of administration**	**Site of administration**	**Precautions**
Infants 6–35 months	Intramuscular	Anterolateral thigh or deltoid muscle if muscle mass is adequate	Do NOT administer by intravascular injection and ensure that the needle does not penetrate a blood vessel
Children ≥ 36 months and adults	Intramuscular	Deltoid muscle	

Due to limited resources, the National Department of Health prioritises certain high-risk groups, making the vaccine available free of charge for them during their annual influenza vaccination campaign; see Table I.[2,16,19,34-38]

Influenza vaccine dosage and administration

Influenza vaccines should be administered before the start of the influenza season, as it takes approximately two weeks to develop protective antibodies.[2,39] It is however never too late to vaccinate, as vaccination will provide protection during the rest of the season.[2,39] The recommended dosages and administration of IIV are summarised in Table II.[2,23-26,34]

The IIV should be stored in a refrigerator between 2–8 °C and should not be frozen.[23-26] The vaccine should be allowed to reach room temperature, must be gently swirled to distribute the suspension uniformly, and be visually inspected for any particulate matter and/or discolouration before use.[23-26]

Contraindications and special precautions

It is important to note that IIV is not recommended for infants aged < 6 months.[2,23-26] Persons with minor illnesses without fever may be vaccinated. Vaccination must however be postponed in the case of fever, or moderate/severe acute illness, with or without fever.[2,23-26]

Vaccination is contraindicated in persons with a history of severe (anaphylactic) hypersensitivity to the IIV or any component of the vaccine.[2,23-26] This includes severe allergic reaction to egg proteins and chicken proteins.[23-25] However, mild egg protein allergy is not a contraindication to influenza vaccination.[2] The Advisory Committee on Immunization Practices in the United States revised their recommendations regarding the use of the influenza vaccine in the case of egg allergy.[40] Persons with a mild egg allergy, who have experienced only urticaria or hives after exposure to egg, may receive the influenza vaccine.[40] No post-vaccination observation period is recommended specifically for egg-allergic persons.[40] Persons who previously had a reaction to eggs, other than urticaria or who required emergency medical intervention, should receive the vaccine in a controlled medical setting where any severe allergic reactions can be managed.[40] As a precautionary measure for all vaccines, patients should be observed (seated or supine) for 15 minutes after administration of the vaccine, to decrease the risk of injury, should syncope occur.[40]

With the exception of the COVID-19 vaccine, the influenza vaccine can be given concurrently with other injectable, non-influenza vaccines but must be administered at different injection sites. Until evidence suggests otherwise, influenza vaccination should be separated by a minimum interval of 14 days before or after administration of the COVID-19 vaccine.[41]

Currently, data on the safety, effectiveness and immunogenicity of influenza vaccines in patients infected with COVID-19 are scarce.[40] However, what is known is that influenza vaccination is safe and does not increase the incidence of COVID-19 or result in increased serious adverse events.[42] Influenza vaccination is recommended once a patient with COVID-19 has substantially improved or has completely recovered.[40]

Adverse events following immunisation

The safety profile of IIV is well established.[2] Side-effects usually present soon after vaccination and last approximately one to three days.[2,30] Most commonly reported side-effects are injection site reactions such as pain/tenderness, erythema/redness, oedema/swelling.[23-26,30] Common systemic side-effects include low grade fever, malaise, rigours/shivering, headache, fatigue, myalgia and irritability.[23-26,30]

More detailed information on the vaccine components, contraindications, precautions and side-effects are available from the individual IIV package inserts.[23-26] Any adverse event of concern (whether minor or severe) should be reported as an adverse events following immunisation (AEFI) to the Expanded Programme on Immunisation (Email: AEFI@health.gov.za). Documentation for reporting is available on the NICD website: https://www.nicd.ac.za/diseases-a-z-index/adverse-event-following-immunization-aefi/ or from the SAPHRA website: https://www.sahpra.org.za/health-products-vigilance/.

Role of healthcare workers in promoting influenza vaccination

All healthcare workers play a key role in ensuring optimal influenza vaccination coverage, hence providing indirect protection to unvaccinated persons in the community through herd immunity.[7,31] Vaccines should be available and accessible to all, but in particular high-risk individuals, including patients at HIV clinics, antenatal clinics, medical outpatient clinics and oncology clinics, and information provided on where vaccination can be accessed free of charge or covered by private health insurance.[2]

A common misconception is that the IIV can result in influenza, hence communication that the vaccine does not contain live viruses and cannot cause disease, is crucial.[30] The possibility of side-effects should be communicated at the time of vaccination, as systemic side-effects such as mild fever and body aches may be wrongly perceived as influenza symptoms.[30] Another misconception is that the vaccine is not effective, because the common cold and other respiratory illnesses contracted during the influenza season are often mistaken for influenza.[30] Furthermore, the effectiveness of influenza vaccination depends on how well the vaccine matches the current season's circulating virus.[18,30,43] Vaccination therefore only protects against vaccine strains and not against many other viruses circulating during the winter season and causing respiratory infections.[18,30] Although vaccine effectiveness in preventing infection is reduced in some high-risk groups, vaccination is highly recommended since the vaccine is very effective in reducing severe influenza complications in these groups.[2]

Misinformation about vaccination in general is spread via social media platforms and the internet.[44,45] Healthcare workers, particularly pharmacists and nurses, can be instrumental in ensuring that their clients are educated and provided with relevant and correct information about the benefits of influenza vaccination for themselves, their children and the community.[45,46]

Healthcare workers are the public's most trusted source of vaccination-related information, thus patients' vaccination decisions can be positively influenced through good communication skills, allowing time to listen and respond to their concerns, and establishing a trusting relationship.[45,46] Providing accurate information and facts about the significant risks associated with not being vaccinated, can help to debunk common misconceptions about influenza vaccination.[45,46]

Conclusion

Annual vaccination remains the first-line defence against influenza. Prevention of severe influenza during pandemics such as COVID-19, can lessen the burden on the healthcare system. Developing a protective antibody response takes approximately two weeks, hence vaccination before winter is advised. AEFI are usually mild and subside within one to three days. The vaccine is inactivated, therefore cannot cause influenza. An important public health role of healthcare workers is to be actively involved in advocating for influenza vaccination and educating the public about the benefits of increased vaccination coverage, for the community and for themselves. Global evidence of the value of influenza vaccination in disease prevention underscores this approach.

References

1. World Health Organization. Influenza (Seasonal). [Internet]. 6 November 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). Accessed 3 Mar 2021.
2. Blumberg L, Cohen C, Dawood H, et al. Influenza NICD recommendations for the diagnosis, prevention, management and public health response. Version 1.3. 2 April 2020. Available from: https://www.nicd.ac.za/wp-content/uploads/2020/04/INFLUENZA-GUIDELINES-2020.pdf. Accessed 3 Mar 2021.
3. World Health Organization. Global Influenza Strategy for 2019-2030. Geneva, World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. Cataloguing-in-Publication (CIP) data. Available from: http://apps.who.int/iris.
4. Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391(10127):1285-300. https://doi.org/10.1016/S0140-6736(17)33293-2.
5. Tempia S, Walaza S, Moyes J, et al. Quantifying how different clinical presentations, levels of severity, and healthcare attendance shape the burden of influenza-associated illness: a modeling study from South Africa. Clin Infect Dis. 2019 Aug 30;69(6):1036-48.
6. Cohen C, Walaza S, Treurnicht FK, et al. In- and out-of-hospital mortality associated with seasonal and pandemic influenza and respiratory syncytial virus in South Africa, 2009–2013. Clin Infect Dis. 2018 Jan 6;66(1):95-103. https://doi.org/10.1093/cid/cix740.
7. Sambala EZ, Ngcobo N, Machingaidze S, et al. A global review of seasonal influenza vaccine introduction: analysis of the WHO/UNICEF Joint Reporting Form. Expert Rev Vaccines. 2019 Aug;18(8):859-65. https://doi.org/10.1080/14760584.2019.1640119.
8. Tempia S, Walaza S, Viboud C, et al. Deaths associated with respiratory syncytial and influenza viruses among persons ≥ 5 years of age in HIV-prevalent area, South Africa, 1998–2009(1). Emerg Infect Dis. 2015 Apr;21(4):600-8.
9. National Institute for Communicable Diseases. Communicable diseases communique. October 2020. [Internet]. Available from: https://www.nicd.ac.za/wp-content/uploads/2020/10/NICD-Monthly-Communiqu%C3%A9_October-2020.pdf. Accessed 5 Mar 2021.
10. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic - United States, Australia, Chile, and South Africa, 2020. Am J Transplant. 2020 Dec;20(12):3681-5. https://doi.org/10.1111/ajt.16381.
11. Centers for Disease Control and Prevention. Types of Influenza Viruses. [Internet]. [Updated 18 Nov 2019]. Available from: https://www.cdc.gov/flu/about/viruses/types.htm. Accessed 3 Mar 2021.
12. Johnson KEE, Song T, Greenbaum B, Ghedin E. Getting the flu: 5 key facts about influenza virus evolution. PLoS Pathog. 2017;13(8):e1006450. https://doi.org/10.1371/journal.ppat.1006450.
13. World Health Organization. Global epidemiological surveillance standards for influenza. Geneva: World Health Organization, 2013. Available from: https://www.who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf?ua=1. Accessed 3 Mar 2021.
14. Department of Health Republic of South Africa. National influenza policy and strategic

plan 2017 to 2021. [Internet]. Available from: http://www.health.gov.za/index.php/component/phocadownload/category/339. Accessed 3 Mar 2021.
15. Centers for Disease Control and Prevention (CDC). Influenza (flu). How flu spreads. [Internet]. [Updated 27 Aug 2018]. Available from: https://www.cdc.gov/flu/about/disease/spread.htm. Accessed 3 Mar 2021.
16. National Institute for Communicable Diseases. Influenza frequently asked questions for parents and caregivers. June 2019. [Internet]. Available from: http://www.nicd.ac.za/wp-content/uploads/2019/06/FAQ_Influenza_For-parents-and-caregivers_20190610.pdf. Accessed 3 Mar 2021.
17. Centers for Disease Control and Prevention. Cold versus flu. [Internet]. [Updated 30 Dec 2019]. Available from: https://www.cdc.gov/flu/symptoms/coldflu.htm. Accessed 3 Mar 2021.
18. World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2021 southern hemisphere influenza season. [Internet]. [Updated 25 Sept 2020]. Available from: https://www.who.int/influenza/vaccines/virus/recommendations/202009_recommendation.pdf?ua=1. Accessed 03 Mar 2021.
19. Tempia S, Walaza S, Moyes J, et al. Risk factors for influenza-associated severe acute respiratory illness hospitalization in South Africa, 2012–2015. Open Forum Infectious Diseases. 2017;4(1):ofw262-ofw262.
20. World Health Organization. Five simple steps to protect against flu. 19 November 2019. [Internet]. Available from: https://www.who.int/news-room/feature-stories/detail/five-simple-steps-to-protect-against-flu. Accessed 3 Mar 2021.
21. National Department of Health (NDoH). Practical Manual for Implementation of the National Infection Prevention and Control Strategic Framework. 2020. Available from: http://www.health.gov.za/index.php/component/phocadownload/category/626. Accessed 28 Mar 2020.
22. McAnerney JM, Cohen C, Moyes J, et al. Twenty-five years of outpatient influenza surveillance in South Africa, 1984-2008. J Infect Dis. 2012 Dec 15;206 Suppl 1:S153-8. https://doi.org/10.1093/infdis/jis575.
23. Influvac® package insert. Abbott Laboratories S.A. (Pty) Ltd. 2020.
24. Vaxigrip Tetra® package insert. Sanofi-Aventis South Africa (Pty) Ltd. 2020.
25. Influvac Tetra® package insert. Abbott Laboratories S.A. (Pty) Ltd. 2020.
26. Fluarix Tetra® package insert. GlaxoSmithKline South Africa (Pty) Ltd. 2020
27. Gresset-Bourgeois V, Leventhal PS, Pepin S, et al. Quadrivalent inactivated influenza vaccine (VaxigripTetra™). Expert Rev Vaccines. 2018 Jan;17(1):1-11. https://doi.org/10.1080/14760584.2018.1407650.
28. Pepin S, Dupuy M, Borja-Tabora CFC, et al. Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6-35 months: A multi-season randomised placebo-controlled trial in the Northern and Southern Hemispheres. Vaccine. 2019 Mar 22;37(13):1876-84. https://doi.org/10.1016/j.vaccine.2018.11.074.
29. Mattila JM, Vuorinen T, Heikkinen T. Comparative severity of influenza A and B infections in hospitalized children. Pediatr Infect Dis J. 2020 Feb 14. https://doi.org/10.1097/INF.0000000000002610. [Epub ahead of print].
30. Centers for Disease Control and Prevention (CDC). Influenza (flu). Misconceptions about seasonal flu and flu vaccines. [Internet]. [Updated 27 Sept 2019]. Available from: https://www.cdc.gov/flu/about/qa/misconceptions.htm. Accessed 20 Mar 2020.
31. Kim TH, Johnstone J, Loeb M. Vaccine herd effect. Scand J Infect Dis. 2011 Sep;43(9):683-9. https://doi.org/10.3109/00365548.2011.582247.
32. World Health Organisation (WHO). WHO SAGE seasonal influenza vaccination recommendations during the COVID-19 pandemic. Interim guidance. 21 September 2020. Available from: https://www.who.int/immunization/policy/position_papers/Interim_SAGE_influenza_vaccination_recommendations.pdf. Accessed 7 Mar 2021.
33. Yang MJ, Rooks BJ, Le TT, et al. Influenza vaccination and hospitalizations among COVID-19 infected adults. J Am Board Fam Med. 2021 Feb;34(Suppl):S179-82. https://doi.org/10.3122/jabfm.2021.S1.200528.
34. National Department of Health. Essential Drugs Programme. Primary Healthcare Standard Treatment Guidelines and Essential Medicines List. 6th ed. National Department of Health; 2018. Available from: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list. Accessed 20 Mar 2020.
35. Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. Lancet Glob Health. 2020 Apr;8(4):e497-e510. https://doi.org/10.1016/S2214-109X(19)30545-5.
36. Thompson MG, Kwong JC, Regan AK, et al. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: a multi-country retrospective test negative design study, 2010-2016. Clin Infect Dis. 2019;68(9):1444-53. https://doi.org/10.1093/cid/ciy737.
37. Walaza S, Tempia S, Dawood H, et al. Influenza virus infection is associated with increased risk of death amongst patients hospitalized with confirmed pulmonary tuberculosis in South Africa, 2010-2011. BMC Infect Dis. 2015;15(1):26.
38. Fezeu L, Julia C, Henegar A, et al. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. Obesity Reviews. 2011;12(8):653-9.
39. McAnerney JM, Walaza S, Cohen C. Flu season is around the corner… Vaccine Focus. March 2019;5(1),10-11.
40. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices - United States, 2020-21 Influenza Season. MMWR Recomm Rep. 2020 Aug 21;69(8):1-24. https://doi.org/10.15585/mmwr.rr6908a1.
41. Centers for Disease Control and Prevention (CDC). Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. [Internet]. [Updated 5 Mar 2021]. Available from: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed 5 Mar 2021.
42. Zein J, Whelan G, Erzurum S. Safety of influenza vaccine during COVID-19. Journal of Clinical and Translational Science. 2020;1-3. https://doi.org/10.1017/cts.2020.543.
43. Schmid P, Rauber D, Betsch C, et al. Barriers of influenza vaccination intention and behavior - a systematic review of influenza vaccine hesitancy, 2005–2016. PLoS One. 2017;12(1):e0170550. https://doi.org/10.1371/journal.pone.0170550.
44. Burnett RJ, Von Gogh LJ, Moloi MH, et al. A profile of anti-vaccination lobbying on the South African internet, 2011-2013. S Afr Med J. 2015 Nov;105(11),922-6. https://doi.org/10.7196/SAMJ.2015.v105i11.9654.
45. Burnett RJ. Dealing with vaccine hesitancy. Paediatric Focus. May 2019;10(1):12-14.
46. Burnett RJ, Larson HJ, Moloi MH, et al. Addressing public questioning and concerns about vaccination in South Africa: A guide for healthcare workers. Vaccine. 2012;30 Suppl 3:C72-8.