In this edition we look at an old friend of the family physician: 'influenza' and the 'flu injection'.

Learning Objectives:
After reading through the material presented, readers should be able to:

- List the components of a virus
- Understand the nomenclature for the different Influenza viruses
- Explain what haemagglutinin and neuraminidase are and what they do
- Know the indications and contraindications for administering the influenza vaccine
- Explain why the influenza vaccine should or should not be given to HIV-infected persons
- Recognise the cost-effectiveness of the influenza vaccine
- Assimilate evidence-based conclusions concerning the prevention and treatment of influenza
- Understand that the influenza vaccine does not cause 'relapses' in multiple sclerosis patients.

Space limitations have meant that some of the material could not be included. This includes the pathophysiology and pathogenesis of influenza as well as complications. The fascinating history of the discovery of the shape of the virus and its particular properties, as well as ongoing research into new therapies was also not included. These aspects are all well-described on several internet sites and well worth following up.

Reporting of Influenza outbreaks
There is an appeal from the National Institute for Virology to all Medical Practitioners working in clinics and hospitals to report any suspected influenza outbreak directly to Dr T G Besselaar at: terryb@niv.ac.za .

Dr Besselaar can also be reached at :
Telephone Number: (011) 321 4269
Fax Number: (011) 882 0596
Postal Address: National Institute for Virology
Private Bag X4
Sandringham 2131

Enjoy this edition's 'Care for Patients and their Disorders'.

Roy Johnson

INFLUENZA

Our patient, Johannes, is a 31 year old man – HIV-positive – who wants to know whether or not he should have a 'flu injection'. The structure of this CPD exercise is as follows:

1. **Back to basics**
   - Viruses and their components
   - Influenza viruses
   - Influenza vaccines
   - Recommendations for winter 2001
2. **Johannes's concerns and questions**
3. **Evidence-based conclusions about influenza vaccines and antiviral agents in the management of influenza.**
4. **Questions for CPD points to be found on the flysheet in the envelope**

Part One: Back to Basics

i) *Viruses and their components*

Viruses are not visible under light microscopy. Our knowledge of their structure has been largely dependent on electron microscopy and X-ray crystallography techniques.

Viruses consist of a nucleic acid—ribonucleic acid (RNA) *or* deoxyribonucleic acid (DNA)— plus a protective coat of protein which may incorporate lipid and/or carbohydrate components. The nucleic acid may be single- or double-stranded, and may be segmented into two or more pieces. Viruses do not have their own mitochondria or ribosomes, so cannot survive or reproduce independently. Their parasitic existence is obligatory.

Viral anatomy[1]

The CAPSID denotes the protein shell that encloses the nucleic acid. It is built of structure units.

STRUCTURE UNITS are the smallest functional equivalent building units of the capsid.

CAPSOMERS are morphological units seen on the surface of particles and represent clusters of structure units.

The capsid together with its enclosed nucleic acid is called the NUCLEOCAPSID.

The nucleocapsid may be invested in an ENVELOPE which may contain material of host cell as well as viral origin.

The VIRION is the complete infective virus particle.

ii) *Influenza Viruses*

Influenza viruses are members of the *Orthomyxoviridae* family. The virus is a single-stranded RNA virus with eight separate segments of ribonucleoprotein (RNP), closely associated with a helix-shaped nucleoprotein (NP). A, B and C influenza types are based on variations in the nucleoprotein. The lipoprotein envelope is lined on its inner side by an antigenic matrix protein (M1).

Influenza types A and B are responsible for epidemics and the occasional pandemic in humans. Type C is rare. A number of influenza A viruses are found in birds and animals.

Embedded in the influenza viral envelope are two kinds of protruding antigenic 'spikes'. One is a glycoprotein called 'haemagglutinin' (HA). The other is 'neuraminidase' (NA). So far 15 hemagglutinin and nine neuraminidase subtypes have been identified in type A influenza virions. Only 3 HA and 2 NA subtypes are common in humans, and they are named accordingly: H1N1, H1N2, H2N2, H3N2 and so on. HA attaches a 'flu' virus to the cell membrane of the respiratory epithelial cell it is infecting. Neuraminidase helps penetrate the membrane allowing viral contents to enter the cell's cytoplasm. It also plays a role in inactivating mucus secretions of endothelial cells so that the viral particles can gain access to them. The NA in the newly manufactured viral particles ensures their expulsion from the cytoplasm and cell membrane of the infected cell.[2]

***Table I:* Nomenclature of influenza strains[3]**

TYPE of influ-enza	TOWN where first isolated	NUMBER of isolates	YEAR of isolation	MAJOR subtype (HA/NA)
A	New Caledonia	20	99	(H1N1)
B	Johannesburg	5	99	--

iii) *Influenza vaccines*

Exposing a person to the HA and NA of different influenza viruses reduces the likelihood of infection and if infection occurs – it reduces the severity of the disease. The frequent development of antigenic variation of the influenza viruses – 'antigenic drift' – is the basis of seasonal epidemics, and the reason for incorporating one or more new strains in each year's influenza vaccine. The vaccine is made from highly purified, egg-grown viruses that have been inactivated. Two forms of inactivated influenza A, and one of influenza B virus are usually combined in the vaccine.

WHO Collaborating Centres monitor the types and subtypes of influenza viruses circulating each season. The components of the vaccine for the following season are based on these observations. A consultation is held in mid-February for the Northern hemisphere, and mid-September for the Southern hemisphere to recommend the formulation for the following year.[5] This means that vaccines are a year 'behind' in terms of the actual viruses, but because antigenic drift results in only minor antigenic change from year to year, the vaccine remains highly effective.

An unpredictable 'antigenic shift' is usually due to genetic recombination of different subtypes of influenza A viruses – usually between human and avian sub-types. The last major antigenic shift occurred in 1968 when H3N2 (Hong Kong) influenza suddenly appeared. A global pandemic could occur if a 'new' virus was efficiently transmitted from person to

person. This may be an explanation of the 1918 flu epidemic in which some 20million people died worldwide.

iv) *Recommendations for winter 2001*[6]

The flu strains recommended for the 2001 southern hemisphere influenza season are:

1. A/New Caledonia/20/99-like (H1N1) [A/New Caledonia/20/99 is suitable as a vaccine strain]
2. A/Moscow/10/99-like (H3N2) [A/Panama/2007/99 is recommended as a suitable vaccine strain]
3. B/Sichuan/379/99-like (B) [Either B/Johannesburg/5/99 or B/Victoria/504/00 are recommended as suitable vaccine strains]

Flu usually occurs from about May until September in South Africa. As flu antibodies take one to two weeks to develop, most recommendations are that the vaccination should be given from mid-March to mid-April. It is important to note, however, that there is no real cut-off date for vaccination, especially as many infections may occur late in the season as well.

Part Two: Our Patient

Johannes has known that he is HIV-positive for two years now. Last year he had a bad winter with several weeks in bed. He does not want a repeat of that this year. He was even ill enough to stop smoking, but unfortunately started again a couple of months after getting better. "Too much stress, Doc."

He wants you to tell him if he should have the 'flu injection'. He wants to know if it won't mess up his immune system, lower his CD4 count (which is high at present) or precipitate AIDS. He wants to know if you can guarantee that the immunisation will prevent him from getting sick this winter.

Question One

What would you say to Johannes?

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Answer One

i) You would recommend that he does have the immunisation. You explain that because influenza can cause both a serious illness and possible complications, vaccination will benefit himself (and many HIV-infected patients like him). [see later]

ii) You explain to him that it will not harm his 'immune system', but will protect him from having to deal with the onslaught of a flu infection. You explain that the immunisation stimulates that part of his immune system that makes antibodies rather than the part of his immune system involved in maintaining his CD4 count. You also explain that because influenza vaccination can produce high enough levels of protective antibodies, the impact on his CD4 count through being exposed to flu is likely to be much less than if he did not have his own antibodies. In the CDC's Morbidity and Mortality Weekly Report of 14 April 2000, it is stated: 'Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease has not been demonstrated among HIV-infected persons following influenza vaccination.'[5]

iii) You tell him that you cannot guarantee he will not get sick this winter because he could be infected with a different kind of upper respiratory tract virus such as respiratory syncitial virus, or he could get a bacterial infection.

iv) You make the point again that his smoking dramatically increases his chances of a winter infection, and that you really would like him to try and stop smoking once more.

Question Two

What information is available about influenza infections in HIV-infected people?

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Answer Two[6]

i) The risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than in the peri-influenza periods in young and middle-aged women enrolled in Tennessee's Medicaid program. In women with other high-risk conditions for influenza complications – including chronic heart and lung diseases – the risk of hospitalization for those with HIV-infection was higher.

ii) Influenza symptoms may be prolonged, with an increased risk of complications, for HIV-infected persons

iii) Influenza vaccination produces substantial antibody titers in HIV-infected persons, such as Johannes, who have minimal AIDS-related symptoms and high CD4+ counts. In patients with advanced HIV disease and low CD4+ counts, influenza vaccine might not induce protective antibody titers.

Question Three

What are the general recommendations about who should receive an influenza immunisation?

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Answer Three

The following groups of people can be classified as high risk for influenza infection:[7]

- People over 65 years. [Note: This is being reconsidered in the USA to include anyone over the age of 50 years.]

- Adults and children with chronic diseases such as chronic lung/heart disease, diabetes, chronic renal (kidney) failure.
- Immune suppressed persons, i.e. those that have a defective immune system.
- Children on long term aspirin therapy. (Reye's syndrome)
- Health care workers.
- Household contacts of high risk individuals as stated above, including children.
- Pregnant woman who are medically at high risk should be vaccinated preferably not before the second trimester.

Vaccination for other Groups[7]

Anyone who wants to protect themselves from the risk of getting influenza can be vaccinated. These include:

- People who provide essential community services
- People in the workforce, since extensive absenteeism due to influenza results in huge economic losses. Small businesses are particularly vulnerable as they may have to close down for a period.
- School children and students, especially residing in dormitories.
- Sportspersons and athletes as they could be prone to viral myocarditis if they do not recover fully before exercising again.
- Travellers travelling from one hemisphere to another may be at risk and should be vaccinated at least 2 weeks before departure. As the appropriate vaccine may not be readily available, amantadine can be prescribed if the patient falls in the high risk category.

Question Four

What is the cost-effectiveness of vaccinating people?

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Answer Four

Studies in South Africa have shown that influenza vaccination could save the medical aid industry more than R53 million (assuming an 80% efficacy of the vaccine). In the work environment the cost benefit ratio was found to be up to 5:1.[7]

Question Five

Who should probably not be given Influenza vaccination?

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Answer Five[7]

- Children under 6 months old
- Individuals with allergies to (chicken) eggs
- Anyone with an allergy to neomycin, or thimerosol (a preservative present in contact lens solutions and flu vaccines)

Question Six

Is a low CD4 count a contra-indication?

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Answer Six

Generally speaking, no. The decision is more dependent on the person's clinical condition. When the CD4 is low however, the vaccine may not be particularly effective.

Part Three: Some of the Evidence

1. One of the most readily freely available sources of evidence-based medicine on the world wide web is the 'Therapeutics Initiative', University of British Columbia Vancouver, Canada. Their emphasis is on 'evidence-based drug therapy'. (www.ti.ubc.ca)

Prevention and Treatment of Influenza A and B[8]

Conclusions:

Prevention: Vaccination in cohort studies lowered rates of hospitalization, serious morbidity and mortality in patients over 60. Amantadine is a second-line preventive agent.

Treatment: Antiviral treatment at the onset of symptoms shows that amantadine reduces fever by one day and oseltamivir and zanamivir reduce duration of flu symptoms by 0.8 – 0.9 day.

Note: The latter two drugs are neuraminidase inhibitors and are not yet available in South Africa.

2. The Cochrane Collaborative Reviews are widely known for their highly focused approach using randomised controlled clinical trials. Not surprisingly several systematic reviews have been undertaken which involve influenza.

Vaccines for preventing influenza in healthy adults[9]

(Last amended on 21 June 1999)

Reviewers' conclusions: Influenza vaccines are effective in reducing serologically confirmed cases of influenza A. However, they are not as effective in reducing cases of clinical influenza. The use of WHO recommended vaccines appears to enhance their effectiveness in practice.

Amantadine and rimantadine for preventing and treating influenza A in adults[10]

(Last amended on 19 February 1999)

Reviewers' conclusions: Amantadine and rimantadine have comparable effectiveness in the prevention and

treatment of influenza A in healthy adults, although rimantadine induces fewer adverse effects than amantadine.
(Note: Rimantadine is not yet available in South Africa.)

Neuraminidase inhibitors for preventing and treating influenza in healthy adults[11]
(Last amended on 05 June 1999)
Reviewers' conclusions: Neuraminidase Inhibitors (NIs) are effective for the prevention and treatment of influenza. Overall NIs are safe, although oseltamivir causes significant nausea.
(**Note:** NIs act against the neuraminidase antigen of influenza virions. They are used for both Influenza A and Influenza B infections. Amantadine and Rimantadine are only effective against Influenza A infections.)

Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes[12]
(Last amended on 07 September 1999)
Background: Oscillococcinum is a patented, homoeopathic medicine. The rationale for its use in influenza comes from the homoeopathic principle of 'let like be cured by like'. The medicine is manufactured from wild duck heart and liver, a well-known reservoir for influenza viruses.
Reviewers' conclusions: Oscillococcinum probably reduces the duration of illness in patients presenting with influenza symptoms. Though promising, the data are not strong enough to make a general recommendation to use Oscillococcinum for first-line treatment of influenza and influenza-like syndrome. Further research is warranted but required sample sizes are large. Current evidence does not support a preventative effect of homeopathy in influenza and influenza-like syndromes.

And finally a word for people with multiple sclerosis patients who wonder about having an influenza vaccination:
The February 1, 2001, issue of the New England Journal of Medicine reports on a controlled epidemiologic study involving various vaccinations and multiple sclerosis. The vaccination history of MS patients who had relapsed between 1993 and 1997 was followed up. The researchers found no association between MS relapses and tetanus, hepatitis B or influenza vaccinations.[13]

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For a review of viral structure and some extraordinary electomicrographic pictures: Stannard LM. Virus Ultra-Structure. http://www.uct.ac.za/depts/mmi/stannard/linda.html