GUIDELINES

ADULT INFLUENZA VACCINATION GUIDELINE

SAMA-SA Pulmonology Society Working Group

Objective. To outline a rational cost-effective protocol for influenza vaccination of adults in South Africa.

Vaccine description. An inactivated (killed) virus vaccine containing three virus strains representing those most likely to circulate in the southern hemisphere during the upcoming winter. Vaccine success depends on the patient's age, immune system status, and degree of similarity of the virus strains contained in the vaccine to those circulating in the community.

Recommendations. Vaccination is:

- potentially beneficial to any individual
- very effective in young otherwise healthy individuals
- targeted at high-risk groups when there is limited availability and cost considerations.

Evidence. Detailed literature review with emphasis on local South African studies.

Benefits, harms, costs. Successful vaccination may be effective in protecting against acute respiratory tract infection, and preventing hospitalisation, complicating pneumonia and death. The vaccine is safe with only occasional reports of anaphylaxis. Contraindications to the vaccine are anaphylactic hypersensitivity to eggs, allergy to other components of the vaccine, and acute severe febrile illness.

Vaccine cost-effectiveness has been confirmed in several groups, including healthy working adults, elderly living in the community, elderly with underlying chronic medical disorders.

Validation. Endorsement by the SA Pulmonology Society, SAMA and all who attended a multidisciplinary consensus meeting to consider the draft guideline.

Financial sponsor. Development supported by an unrestricted educational grant by Pasteur Mérieux Connaught to SAMA.

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GENERAL INTRODUCTION

Infections with the influenza virus and *Streptococcus pneumoniae* are associated with considerable morbidity and mortality, both in developed and developing countries. Although vaccines are available for the prevention of both these infections, concerns about their safety, efficacy and cost-effectiveness have resulted in limited use in the community. While both vaccines have been shown to be highly effective in preventing these infections in young healthy individuals, because of availability and cost considerations most international recommendations for vaccine use target the elderly and certain other groups of patients who are at increased risk of acquiring these infections and their associated complications. The purpose of this guideline is to provide rational and cost-effective recommendations for influenza vaccination in adults in South Africa.

ABBREVIATIONS

AIDS = acquired immune deficiency syndrome; CDC = Centers for Disease Control and Prevention, Atlanta, Georgia; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CSF = cerebrospinal fluid; H = haemagglutinin; HIV = human immunodeficiency virus; ICU = intensive care unit; MIC = minimum inhibitory concentration; N = neuraminidase; RNA = ribonucleic acid; SA = South Africa; SAMA = South African Medical Association; SAPS = South African Pulmonology Society; USA = United States of America.

LEVELS OF EVIDENCE

In this guideline the following levels of evidence have been used to indicate the strength of the supporting research.

Evidence level	*Description*
A	Very good evidence of efficacy of the vaccine including data from studies at least one of which is a prospective, randomised, double-blind, placebo-controlled trial.
B	Good evidence of efficacy of the vaccine including data from prospective cohort studies and retrospective case-control trials.
C	Efficacy of the vaccine is not consistently demonstrated, but the high risk for disease as well as the potential benefit and the safety of the vaccine justify its use in the circumstances.

METHODOLOGY

This project was initiated by C Feldman of the SAPS and a collaborative venture with the SAMA Centre for Quality Care was established. Funding was obtained from Pasteur Mérieux Connaught (Rhône-Poulenc Rorer) in terms of an unrestricted

educational grant. A draft guideline was developed in conjunction with the authors.

On 20 February 1999 a nationally representative adult respiratory vaccinations consensus meeting was held in Gauteng (see below). Participants were invited as representatives of professional, government and consumer groups with an interest in the adult respiratory vaccination field. Each organisation so invited nominated its own representatives. All participants received a copy of the draft guideline developed previously together with the relevant references before the meeting. The meeting was chaired by a neutral chairperson. The purpose of the meeting was to consider the content of the draft guideline and either endorse or amend the document. The proceedings were audio recorded and transcribed for future reference.

The endorsement document was revised according to the proceedings of the national consensus meeting. The endorsement draft document was circulated to all participants and many other interested persons. The endorsement draft was also available on the Centre for Quality Care's Internet site, via SAMA-online for further comment. (**www.samedical.org/cqc**)

Amendments to this endorsement draft were made where there was sufficient need as indicated by the comments received. All major debates and areas where it was not possible to come to agreement were highlighted. The document as revised was submitted to SAMA's Guideline Committee for endorsement according to the set criteria. Once endorsed the guideline was sent for publication to the *South African Medical Journal*. The guideline will also be available in the compendium and on the SAMA Centre for Quality Care's Internet site.

The grants were made in accordance with the SAMA code of sponsorship which precludes attempts by sponsors to unethically influence the content of the guideline. All funds were paid directly into SAMA's accounts and all disbursements were made from that fund.

SAMA-SAPS Adult Respiratory Vaccinations Working Group

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*A number of working group members have been nominated by more than one professional group.

1. Introduction[1-6]

The influenza virus is a serious respiratory pathogen which causes significant morbidity and even mortality during the winter months, particularly in the elderly and in special high-risk groups. It has been estimated that the annual attack rate is between 10% and 20%. The main method of prophylaxis is immunisation, and successful influenza vaccines are available each year for the predominant serotypes of the virus.

2. The virus[2,6-9]

The influenza viruses are enveloped viruses with a segmented RNA genome. There are three types, influenza A, B and C, based on antigenic differences. Both influenza A and B viruses may cause severe disease, while influenza C virus more commonly causes mild upper respiratory tract infections. Influenza A viruses are classified into subtypes on the basis of two surface antigens:

- haemagglutinin (H: which has subtypes, e.g. H1, H2, H3) and
- neuraminidase (N: which has subtypes, e.g. N1 and N2).

Immunity to these antigens, especially the haemagglutinin, reduces the chance of infection as well as the severity of the infection if it does occur. Both influenza A and B undergo antigenic variation. Because of antigenic variation major epidemics of respiratory disease caused by new variants of influenza continue to occur. The antigenic characteristics of the circulating strains provide the basis for selecting the virus strains to be included in each year's vaccine.

3. Risk factors for complicated infection[1,5,8,10-18]

The main underlying disorders associated with increased risk of complications from influenza are chronic respiratory and cardiac conditions.

- **Cardiorespiratory disorders** account for up to 80% of the cases with high-risk conditions during influenza epidemics, and the highest rate and greatest risk for complications are in persons > 65 years.
  - **Respiratory disorders** include chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis. Although asthmatics do not appear to have increased susceptibility to viral infections they are likely to develop a more severe response to such infections. Influenza infections occurring in patients with chronic lung disease may be associated with acute exacerbations of asthma or COPD, greater need for hospitalisation, complicating pneumonia, and even death.
  - **Cardiac conditions** associated with congestive cardiac failure are important risk factors for complicated influenza infections and have a particularly high risk of death.
- **Chronic conditions** associated with an increased risk of complicated infection include:
  - chronic metabolic conditions such as diabetes mellitus
  - chronic renal dysfunction
  - immune deficiency.
- **Residents of chronic care facilities, rehabilitation institutions and nursing homes, particularly those with underlying chronic medical disorders** are at increased risk of complicated infections. In these situations the infection spreads very rapidly once the virus is introduced into the population.
- **Pregnant females.** It has been documented that influenza mortality has been higher in pregnant females during some previous influenza epidemics.
- **HIV-seropositive individuals.** Influenza is more prolonged and more severe.

4. Control of influenza

Two measures available that can reduce the occurrence and impact of influenza are immunoprophylaxis with inactivated (killed) virus vaccine and chemoprophylaxis with an influenza-specific antiviral drug (amantadine).

4.1 Influenza vaccine[2,3,6,8,15,18-22]

Inactivated influenza vaccines are currently prepared from virions produced in embryonated chicken eggs. Three types are available:

- **whole virus vaccine** — partial purification of the virus followed by chemical inactivation
- **split-product vaccine** (subvirion) — further treatment of the virion to disrupt the virus envelope, and
- **partial purified haemagglutinin/neuraminidase subunit vaccines** (purified surface antigens).

The immunogenicity and protective efficacy are similar, but whole virus vaccines are not recommended for children < 12 years of age because of increased febrile reactions. In children, split-product or subunit vaccines are recommended.

Each year's influenza vaccine contains three virus strains (usually two type A and one type B) representing the viruses likely to be circulating in the country during the upcoming winter. The vaccine is made from highly purified egg-grown viruses that have been inactivated. Most vaccinated individuals develop high post-vaccination haemagglutination-inhibition antibody titres which are protective against strains similar to those in the vaccine. The influenza vaccine is effective against acute respiratory tract infections as well as being effective in the prevention of pneumonia, hospitalisation and death. While vaccination may not totally prevent the development of influenza infection, if this infection does occur following vaccination the course is usually milder. Elderly patients or individuals with underlying chronic diseases may develop lower post-vaccination antibody titres and thus remain susceptible to influenza-related upper respiratory tract infections, although they may still be protected against lower respiratory tract infections or other secondary complications.

The effectiveness of the vaccine also depends on the degree of similarity of the virus strains included in the vaccine to those circulating during the influenza season. When there is a good match between the two, influenza vaccine has been shown to prevent infection in approximately 70 - 90% of healthy persons < 65 years of age. In similar circumstances, the effectiveness of the vaccine in preventing hospitalisation for pneumonia and influenza in the elderly living in old-age homes and frail-care centres ranges between 30% and 70%. In the elderly living in nursing homes, the vaccine is 50 - 60% effective in preventing hospitalisation and pneumonia and 80% effective in preventing death even though it may only be 30 - 40% effective in preventing influenza infection itself.

4.2 Recommendations for vaccination[2,3,6,8,18,21-24]

Vaccination is recommended for:

- all persons ≥ 6 months of age who, because of age or underlying disease, are at increased risk for influenza and its complications
- health care workers and others (e.g. household members) in close contact with persons in the high-risk group
- individuals providing essential services, and
- persons living or working in special circumstances in which the virus may spread rapidly.

The composition of the vaccine that is recommended for the winter season is changed on a yearly basis. Strains are selected in September of the preceding year by the Southern Hemisphere Network for Influenza and the World Health Organisation Collaborative Centre for Influenza in Melbourne,

Australia. For example, the influenza vaccine recommended for the 1999 season in the southern hemisphere contained the following three components:[23,25]

- an A/Sydney/5/97(H3N2)-like virus
- an A/Beijing/262/95(H1N1)-like virus
- a B/Harbin/7/94-like virus.

The formulation of the recommended vaccine appears on the Internet as soon as this decision has been made and is published in the *South African Medical Journal* in February of every year.

During delivery and storage, the vaccine should be kept at 2 - 8°C in cold chain, and stored in the fridge and not the freezer. The vaccine should not be kept at room temperature for > 8 hours and should be kept out of the reach of children.

The influenza season in the southern hemisphere normally runs from April to October. Most of the adult population is likely to have been previously infected with influenza A (H3N2), influenza A (H1N1) and influenza B and to have some degree of residual immunity. As a consequence only one dose of influenza vaccine should be sufficient for all ages except young children. The vaccine may be administered by anyone legally allowed to do so. Administer as a single dose of 0.5 ml intramuscularly using the deltoid muscle in older children and adults. The vaccine can be given at the same time as the pneumococcal vaccine, but in different arms. The optimal timing of the vaccine is in early April in order to ensure adequate antibody titres prior to the onset of the influenza season and for the duration of winter. Since occasional episodes of anaphylaxis occur, adrenalin (1:1 000) should be readily available.

4.3 Target groups for vaccination[2,3,6,8,18,23,24,26,27]

The vaccine may be of benefit to any individual and has been shown to be highly effective in young, healthy adults. Nevertheless, because of limited availability and cost considerations, certain groups are specifically targeted to receive the vaccine. Target groups for routine annual influenza vaccination are shown in Table I. The levels of evidence for the recommendations are indicated in brackets (for a summary of the evidence levels see p. 1216). Individuals for whom routine annual vaccination is recommended include:

- **Persons ≥ 65 years of age** (level A).
- **Adults and children with chronic disorders of the cardiorespiratory system.** This includes patients with asthma, chronic obstructive pulmonary disease and cardiac conditions associated with cardiac failure (level B).
- **Adults and children who have required regular medical follow-up or hospitalisation because of chronic metabolic diseases** (e.g. diabetes mellitus), renal dysfunction, or immunosuppression (including that due to medication). These patients are at increased risk of acquiring influenza as well as its complications (level B).
- **Residents of nursing homes, frail-care centres, old-age homes and rehabilitation institutions** that house persons of any age with chronic medical conditions (level B).
- **Groups that may transmit influenza to persons at high risk** should also be vaccinated, including doctors, nurses and other personnel in both hospital and outpatient care settings, employees of chronic care facilities and nursing homes who have contact with patients or relatives, providers of home care to patients at high risk and household contacts of persons at high risk (level A evidence for protection of these otherwise healthy contacts, level B evidence for protection of high-risk individuals).
- **Other groups.** Persons providing essential community services (especially emergency and security personnel) should be considered for vaccination. Persons living in circumstances where influenza would spread rapidly, including mining compounds, military barracks and prisons, and students and other persons living in institutional settings (e.g. dormitories), should be considered for vaccination. Persons who work in circumstances where influenza may spread rapidly, such in large companies, should be considered for vaccination (level A).

Table I. Target groups for routine annual influenza vaccination (levels of evidence given in brackets)

Groups at increased risk for influenza-related complications
- Person ≥ 65 years of age (A)
- Adults and children with chronic cardiorespiratory disorders including: asthma, chronic obstructive pulmonary disease, cardiac conditions associated with cardiac failure (B)
- Adults and children requiring regular health care follow-up or hospitalisation due to chronic medical illnesses including metabolic disorders (e.g. diabetes mellitus), renal dysfunction, immunosuppression (B)
- Residents of nursing and old-age homes, frail-care centres, rehabilitation institutions housing persons of any age with chronic medical conditions (B)

Groups that can transmit influenza to high-risk persons
- Health care personnel in hospital and outpatient setting (A)
- Employees of hospitals and chronic care facilities (A)
- Providers of home care for high-risk persons (A)
- Household contacts of high-risk persons (A)

Vaccination should be considered in the following groups
- Those who provide essential community service especially emergency and security personnel (A)
- Those living/working in special circumstances where influenza may spread rapidly (e.g. mine compounds, military barracks, prisons, dormitories, large workforces) (A)

Contraindications to influenza vaccination
- Anaphylactic hypersensitivity to eggs
- Allergy to other components of the influenza vaccine
- Acute severe febrile illness, until symptoms subside

- **Persons travelling to other areas.** For example, persons travelling to the northern hemisphere during the influenza season, particularly those in high-risk categories, should be encouraged to receive the most current vaccine appropriate to the northern hemisphere. This is available in South Africa on specific request.
- **Pregnancy.** The CDC has recommended that pregnant women in the second or third trimester of pregnancy should be considered for vaccination. There is some evidence that women, particularly in the third trimester of pregnancy and in the puerperium, are at increased risk of serious complications of influenza, even in the absence of additional underlying risk factors. It has therefore been recommended that influenza vaccination should be considered in pregnant women who will be in their second or third trimester of pregnancy during the influenza season, and that the vaccine should be considered in all pregnant women who have medical conditions that increase their risk of complications, irrespective of their trimester, before the start of the influenza season. Although definitive studies have not been conducted, the influenza vaccine is considered to be safe in pregnancy. Influenza vaccine does not affect the safety of breast-feeding for mothers and infants and also breast-feeding does not adversely affect the immune response and is not a contraindication to vaccination. These indications are undergoing scrutiny at the current time. As evidence emerges to support these recommendations, changes will be made to the guideline and these will appear rapidly on the Internet site (**www.samedical.org/cqc**)
- **Persons with human immunodeficiency virus (HIV) infection.** Limited data are available with regard to the effects of influenza on the HIV-infected individual, but there is some evidence that symptoms may be prolonged and complications more common, at least in some cases. As indicated with the pneumococcal vaccine, transient (2 - 4 week) increases in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after influenza vaccine have been noted in some studies. These increases are of uncertain significance. In keeping with the caution noted with pneumococcal vaccine, routine vaccination of HIV-seropositive individuals with influenza vaccine is not recommended until further studies have been undertaken. These indications are undergoing scrutiny at the current time. As evidence emerges to support these recommendations, changes will be made to the guideline and these will appear rapidly on the Internet site (**www.samedical.org/cqc**)

4.4 Persons who should not be vaccinated[2]

The vaccine should not be administered to any individual known to have severe anaphylactic hypersensitivity to eggs or to any of the other components of the influenza vaccine. Information on vaccine components is contained in the package insert. Minor egg allergy may not be an absolute contraindication to vaccination, and the potential benefits of vaccination in each individual should be balanced against the probability of a significant reaction. When in doubt, a specialist opinion (e.g. physician, infectious disease specialist, immunologist) is advised. Adults with acute febrile illnesses should not be vaccinated until their symptoms have abated, although minor illnesses should not contraindicate the use of the vaccine. Contraindications to influenza vaccination are shown in Table I.

4.5 Side-effects and adverse reactions[2,8,16-18,28-34]

The most frequent side-effect is soreness at the vaccination site, lasting up to 2 days. Two types of systemic reactions have been noted:

- Fever, malaise, myalgia and other systemic symptoms in persons not previously exposed to the vaccine antigens which begins within 6 - 12 hours and lasts 1 - 2 days.
- Immediate, presumably allergic, reactions occur rarely.

Patients should be warned about the possibility of febrile reactions. However, they should also be assured that because the vaccine is an inactivated killed virus they are not at any risk of developing influenza from the vaccine. While febrile reactions are usually due to reactions to components of the vaccine they may occasionally be due to intercurrent unrelated infections.

There has been concern that vaccination may be associated with acute exacerbations of asthma, since it is well known that viral infections are a common precipitant of asthma, particularly in children. However, the bulk of the published literature suggests that there is little evidence of impairment of lung function or of acute exacerbations occurring in patients with asthma who receive the killed vaccine. In general whole virus vaccine is more likely to be associated with side-effects than split virus or subunit vaccines, and studies of the use of the latter vaccines in asthmatics have shown no serious side-effects. A recent study documented a fall in peak flow of several asthmatics following vaccination but concluded that the risk of pulmonary complications was very small and was outweighed by the benefit of vaccination.

The 1976 swine influenza vaccine was associated with an increased incidence of Guillain-Barré syndrome. A further slight increase in frequency of Guillain-Barré syndrome was also seen in 1990 - 1991. Subsequent vaccines prepared from other strains have not been clearly associated with this syndrome. However the risk, if any, is very low and if it does occur, the risk is less than that for severe influenza that could be prevented by vaccination.

4.6 Antiviral agents for influenza A[2]

Amantadine hydrochloride is an antiviral agent with specific activity against influenza A. It interferes with the replication of type A but not type B influenza virus and when administered prophylactically to otherwise healthy adults is approximately 70 - 90% effective in preventing illness with naturally occurring strains of influenza A. In otherwise healthy adults, it may reduce the severity and duration of symptoms and signs of influenza A infection when administered within 48 hours of onset of illness. It does not interfere with the antibody response to the vaccine and individuals may be vaccinated against influenza while receiving the drug. This drug is scarcely used for prophylaxis in South Africa at the present time because most practitioners are not aware of this indication.

Chemoprophylaxis is not a substitution for vaccination and patients who receive chemoprophylaxis should also be vaccinated unless there is a contraindication. Following such vaccination chemoprophylaxis should be continued for 2 weeks to allow the development of protective antibody levels. The usual dosage in adults is 200 mg daily given in two divided doses (100 mg 12-hourly). The cost is approximately R2 per capsule. Chemoprophylaxis may be considered for the following persons who have not yet been vaccinated:

- high-risk cases after influenza A activity has begun
- contacts and providers of care for high-risk persons
- persons in whom influenza vaccine is contraindicated
- persons who are to travel to other areas, e.g. northern hemisphere.

When confirmed or suspected outbreaks of influenza A occur in institutions that house patients at high risk, chemoprophylaxis should be started as early as possible to limit the spread of the virus. The drug should be continued for 2 weeks or for 1 week after the end of the outbreak. Chemoprophylaxis should also be considered in this situation for unvaccinated staff.

Amantadine hydrochloride can cause both CNS and gastro-intestinal side-effects. These are usually mild and disappear with discontinuation of the drug. Occasionally more serious side-effects occur, including marked behavioural change, delirium, hallucinations, agitation and seizures, particularly with high plasma concentrations. Modification of dosages may be needed in persons with impaired renal and liver function, in the elderly and in children, and in persons with a history of seizures. Dosage recommendations in these different settings are detailed in the package insert.

4.7 Cost-effectiveness[3,13,15,18,26,27,35-38]

A number of studies have investigated cost-benefit and cost-effectiveness of the influenza vaccine and in general the vaccine is cost-saving. Vaccination has been shown to have cost benefits in healthy working adults, including health care workers, in the elderly living in the community, and in the elderly with various underlying chronic medical disorders. Studies in South Africa confirm that vaccination minimises work absenteeism in winter and that routine influenza vaccination will reduce direct and indirect costs of influenza in this country.

4.8 Strategies for implementation of the influenza vaccine[2,18,39,40]

A number of recommendations have been made for successful implementation of influenza vaccination.

- It is essential to educate health care workers and the public at large about the potential benefits of vaccination.
- Individuals in whom vaccination is recommended could be identified in various settings including physician's offices, outpatient clinics, casualty departments, long-term care facilities, acute care hospitals, district nursing services and travel clinics.
- Administrators of health care facilities, large institutions and workplaces should be encouraged to organise for their personnel to be vaccinated.
- Health care funders should be encouraged to meet the demand for vaccination and be made aware of the cost-effectiveness of these measures.

5. DISCLAIMER

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent research and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.

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