

INFLUENZA PANDEMIC PREPAREDNESS

- A CONCEPT PLAN TO PREPARE FOR THE CONTINGENCY OF A MAJOR GLOBAL PANDEMIC OF INFLUENZA

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SECTION I

INTRODUCTION

The WHO and health authorities worldwide have recognized that the world is under threat of a major pandemic of influenza which could potentially have serious effects on the health of the human population. Major pandemics have occurred in 1889, 1918/19, 1957 and 1968 and another major pandemic may well occur in the near future. The 1918/19 pandemic of influenza was one of the most devastating epidemics of an infectious disease to have affected mankind. This pandemic was directly responsible for over 20 million deaths, more than perished in conflict in the preceding Great War, and mainly affected previously healthy young adults. In South Africa the pandemic killed over 300 000 persons, overwhelming the ability of the authorities to dispose of the corpses, in addition to the total paralysis of the healthcare facilities for treating patients. Following on this epidemic there was, also, considerable post-epidemic morbidity in the form of encephalitis lethargica. Unfortunately science has not yet developed the tools to be able to predict when and where a future major pandemic will occur or what the impact of it will be. For this reason countries throughout the world have been invited to prepare contingency plans in the event of a future major pandemic. Were such an event to occur in the future, this would result in a vast demand for vaccine which could result in inequitable distribution as well as major demands for drugs such as antivirals and antibiotics. South Africa may be in a particularly vulnerable position with respect to having to compete with northern hemisphere countries for limited supplies of these materials. To add to this, such a pandemic would potentially make very serious demands on the healthcare system and create a great deal of public consternation. It is for these reasons that the following pandemic plan has been put forward for consideration as a provisional working document with which to implement contingency plans. The WHO has established an influenza pandemic task force to prepare a "blueprint plan" to guide governments in preparing for the next pandemic. Account will need to be taken of this document when it does appear, probably towards the end of this year, in finalizing a definitive pandemic preparedness plan.

SECTION II

THE THREAT OF A MAJOR INFLUENZA PANDEMIC

a) DEFINITION OF A MAJOR PANDEMIC

- , Influenza virus causes outbreaks of influenza every winter season. These outbreaks are of variable intensity but usually affect between 5-30% of the population resulting in a highly variable degree of morbidity and some mortality which is virtually confined to elderly individuals, especially those with underlying medical conditions.
- , When significant antigenic variation occurs in the virus (see Section III) so that the population is largely susceptible, significantly greater epidemic activity occurs which is often global in extent, with varying intensity in different countries often depending on population immunity. These widespread epidemics of influenza are sometimes referred to as pandemics because of their global activity.
- , The major pandemics of influenza are, however, rare events but have dramatic and very major implications. These occur as a result of antigenic shift (see Section III) and because there is a radical change in the antigenic composition of the virus the population is highly susceptible.

For the purposes of this document the term **major pandemics** will refer to the latter pandemic influenza activity which is due to antigenic shift of the virus or to the re-appearance of a novel subtype of influenza virus (see Section III).

b) CHARACTERISTICS OF A MAJOR PANDEMIC

- , Major pandemics are characterized by the following features:-
 - < They are rare events - previous major pandemics occurred in 1889; 1918/19 (the Spanish flu); 1957 (the Asian flu) and 1968 (the Hong Kong flu).
 - < Their appearance is unrelated to season. In the case of more conventional influenza epidemics their appearance is virtually confined to the winter season and isolations are rare outside of winter. Major pandemic influenza, however, can occur at any

season of the year.

- < Epidemic activity spreads very rapidly and is unaffected by season. Conventional influenza epidemics spread over a period of about 18 months and are largely confined to the hemisphere which is in the winter season. This provides ample time for vaccines to be designed and formulated with strains corresponding to the circulating strains. Major pandemics have spread far more rapidly and have penetrated globally within about 9 months, and the spread is unaffected by seasonal influences.
- < The clinical expression of global pandemics may be completely different to conventional influenza epidemics. In the latter epidemic infection is very common in school children and young adults but severe morbidity and mortality occurs mainly in the elderly. In major pandemics there is a completely different pattern of illness. In the 1918/19 pandemic healthy young adults were mainly affected and the elderly were largely spared. In the 1957 pandemic, again school children and young adults were mainly affected. Another important difference between conventional epidemics and major pandemics is that in major pandemics the morbidity and mortality is far greater.

c) THE UNPREDICTABILITY OF MAJOR PANDEMICS

- , Major pandemics have arisen at intervals varying from 29 years (1889-1918), 38 years (1919-1957) and 11 years (1957-1968). It is 29 years since the last major pandemic. There is no scientific methodology of predicting when the next pandemic will arise.
- , Major pandemics are assumed to arise predominantly from the Far East - however the origins of the most devastating of all the pandemics, the 1918/19 pandemic, which was first recognized in Spain (hence the colloquial term "Spanish flu") is still unknown.
- , The severity of major pandemics has been variable. The 1918/19 pandemic was particularly catastrophic and there is considerable evidence to support the supposition that the responsible strain causing that pandemic was super virulent - the intensity of the morbidity and mortality and its effect predominantly in young adults rather than the more frail elderly section of the population would tend to support this.

In addition, a great deal of post-influenza morbidity was observed, particularly encephalitis lethargica. The effects of the 1918/19 pandemic were far in excess of that which could have been due to the non-availability of antibiotics and other forms of treatment in those days. There is, in addition, no record of any similar epidemic of influenza having caused anywhere near the extent of devastation that the 1918/19 pandemic was responsible for.

, The nature of the forthcoming new pandemic strain is unpredictable. It could be a recirculation of a defunct subtype, e.g. H₂N₂ or it could be one which may have previously circulated in humans but for which there are no records extant. Alternately a novel subtype may well be introduced into humans from animal sources, particularly from the pig "mixing bowl" (see Section III).

, Even if a new subtype does arise in humans, this is still not predictive of a major pandemic. For example, the reappearance and reintroduction of H₁N₁ subtype in 1977 did not result in a major pandemic and the appearance of the swine influenza subtype in military recruits in Fort Dix, USA, in 1986 did not spread beyond the confines of that area.

, The opening up of China with increased trade and travel links plus the rapidity and the vast scale of international travel, would further complicate and increase the difficulty of predicting the natural history of a future pandemic.

SECTION III

BACKGROUND INFORMATION: INFLUENZA VIRUS: INFLUENZA: INFLUENZA VACCINES & INFLUENZA CHEMOTHERAPY

1. INFLUENZA VIRUS

a) INTRODUCTION

The influenza virus, like most RNA viruses, is genetically highly variable and this variability gives rise to a constant changing of the antigenicity of the virus. This, in itself, is not peculiar to influenza. However, what is unique to the virus is that this antigenic changeability constantly gives rise to new strains of virus which are able to escape the immunity which the population builds up to the predecessor strain which it now replaces. The epidemiology of influenza is thus characterized by the constant advent of new antigenic strains of the virus giving rise to recurring epidemics of infection.

b) CLASSIFICATION OF INFLUENZA VIRUSES

i) Influenza is classified into 3 **types** based on the antigenicity of a protein called nucleoprotein which intimately surrounds the RNA genome of the virus. As it is an internal protein it is not variable. The 3 types are referred to as type A, type B and type C. (Type C causes a rather trivial mild upper respiratory tract infection and is therefore not a component of influenza vaccine.)

ii) Type A influenza virus is further subdivided into **subtypes** based on the antigenicity of the 2 proteins embedded in the envelope of the virus which are used to attach and to penetrate into the host cell. These are haemagglutinin (HA) (so named because the protein agglutinates red blood cells which forms the basis of the serological test to identify the virus using specific antisera - the haemagglutination inhibition or HI test) and neuraminidase (NA) (so named because this protein is an enzyme which digests the neuraminic acid receptor of the cell to allow the attached virus to penetrate into the cell).

A number of haemagglutinins and neuraminidases have been described in nature but so far only 3 HAs, H₁, H₂ and H₃, and 2 NAs, N₁ and N₂, have been found in man and indeed only 3 subtypes have infected humans, H₁N₁, H₂N₂ and H₃N₂. At present 2 of the subtypes are circulating in humans, H₁N₁ and H₃N₂.

- (iii) Each of the type A subtypes as well as the type B type are, in turn, subdivided into **strains** based on the antigenicity of the HA protein (using more specific antisera, as will be discussed below, than that used for subtyping). The strains are designated according to a formula which describes its full pedigree, i.e. its type, subtype, geographical location of where it was first isolated and the year of isolation. Hence the virus strains incorporated into the 1997 vaccine were designated as A/Texas/36/91 (H₁N₁), A/Wuhan/359/95 (H₃N₂), B/Beijing/184/93 OR B/Harbin/07/94. [The additional number before the year of isolation is merely a laboratory identification number.]

Schematic diagram of influenza virus showing haemagglutinin (HA) and neuraminidase (NA) protein spikes embedded in the envelope and nucleoprotein (NP) surrounding each of 8 pieces of RNA genome.

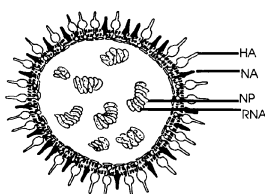
(Illustration: Dr JGM Sim, National Institute for Virology)

c) **THE MECHANISMS OF INFLUENZA VIRUS VARIABILITY**

There are 2 ways in which influenza virus can change its antigenicity, the one, a rare but dramatic event and the other a very much more common and subtle change.

i) **Antigenic Shift**

Influenza virus is one of the few viruses where the individual genes occur on separate and discrete pieces of nucleic acid instead of the more usual complete single strand for the whole genome. As a result of this if two different subtypes happen to infect the same cell, genes from different origins may be swapped when the progeny virus is put together in the assembly phase of the virus' replication. Usually the alien gene or genes will produce an inconsequential hybrid progeny virus which cannot survive or be propagated. This process is called reassortment and the hybrid offspring are referred to as reassortants. The primary mixing bowls where reassortment is



thought to take place in nature are the vast flocks of wild birds, including water fowl, found in China with the pig acting as an intermediate host for man. In China and the Far East the enormous human populations come into close contact with these animal reservoirs who harbour a great variety

of influenza subtypes. Nevertheless, reassortment producing a new human virus is a rare event, happening about once every 10-40 years. When it does occur, it gives rise to a completely new subtype of virus (acquiring a totally new HA and sometimes a new NA protein as well) to which the human population will be readily susceptible and this would then result in the dramatic and sudden classical pandemics such as the 1918/19 Spanish flu pandemic, the 1957 Asian flu pandemic and the 1968 Hong Kong flu pandemic. The sudden and major change in antigenicity of the virus is hence called antigenic shift.

ii) **Antigenic Drift**

This is a more subtle change in the antigenicity of the HA protein - the protein involved specifically in the critical attachment of the virus to its receptor on the host cell. Thus, even subtle changes (i.e. sometimes only 1 or 2 amino acids) may enable the virus to elude the host's immunity. These HA mutations occur readily and continually. Point mutations (i.e. substitution of 1 amino acid) usually do not translate on their own into a significant antigenic change. However, accumulation of these point mutations under the selective pressure of antibodies formed in innumerable human hosts will eventually produce meaningful antigenic change resulting in a virus which can then spread throughout the human population, causing widespread epidemic activity. This more gradual but progressive change is thus called antigenic drift and it gives rise to new antigenic strains of influenza approximately every 3-5 years.

2. **MONITORING INFLUENZA**

a) **THE NETWORK FOR MONITORING ANTIGENIC DRIFTS**

The regular monitoring of human influenza virus isolates for the more regular antigenic drifts is carried out by some 125 national influenza centres throughout the world. These laboratories obtain influenza virus isolates either from routine patient diagnostic material sent into clinical virology laboratories or, alternately, specimens are actively recruited from sentinel medical practitioners or clinics who purpose-fully take throat swabs from patients with upper respiratory tract infections. (A successful viral watch programme with a network of 16 sentinel

practitioners has been operating successfully on the Witwatersrand since 1982.) Preliminary characterization of influenza isolates is carried out by the national centres and these are then sent to one of three WHO Collaborative Centres for Reference and Research on Influenza. These are situated in the CDC, Atlanta, USA, the National Institute of Medical Research in London and the Commonwealth Serum Laboratories in Melbourne, Australia.

b) **ANTIGENIC CHARACTERIZATION OF INFLUENZA ISOLATES**

Influenza virus isolates have classically been antigenically characterized using banks of antisera produced by the WHO reference centres. These antisera are prepared by infecting ferrets with the specific strains of virus to be analyzed and the reactivities against the same, as well as related strains are examined by means of an HI test. More recently, sequencing of the gene coding for the haemagglutinin has been added as a more sensitive technique to chart the evolution of the virus.

c) **THE FORMULATION OF THE INFLUENZA VACCINES**

Once a year, towards the end of the northern hemisphere influenza season, a meeting is convened by the WHO consisting of representatives of the reference centres and other influenza experts, to review the past influenza season and to examine laboratory data on the antigenicity of new isolates. On this basis an estimate is made which strains in each of the A subtypes and the B influenza type virus are likely to circulate in the population the following influenza season. Prototype influenza strains are then selected and used for preparing seed virus strains for vaccine manufacturers to process into vaccines. Influenza vaccines are inactivated (killed) vaccines made by inoculating fertilized chicken eggs with influenza virus, harvesting the fluid and then extensively purifying out the virus which is then chemically inactivated, usually with formaldehyde, to inactivate the virus. (In a further refinement of production the HA protein is biophysically and biochemically purified and used as a subunit vaccine.)

The formulation of the vaccine is announced annually on the last Friday of February in the WHO publication, the Weekly Epidemiological Record. This then allows for approximately 4-5 months for manufacturers to produce and bottle vaccine in time to vaccinate the northern hemisphere population before the onset of their winter.

A global review of influenza viruses is also published in the last week of September of each year for the purpose of providing information for

southern hemisphere formulation. However, the reason for the establishment of a third WHO reference centre in Australia was specifically for the purpose of analysing southern hemisphere isolates in order to produce a formulation specifically for this hemisphere. The southern hemisphere group meet towards the end of September of each year to similarly produce a southern hemisphere vaccine formulation.

d) **WHY THE NEED FOR A SOUTHERN HEMISPHERE VACCINE FORMULATION?**

Epidemics of influenza are temporary, usually lasting for some 8-12 weeks, and always occurring in winter. (In South Africa, virus isolations rarely begin before mid-May and rarely continue beyond mid-September). In the northern hemisphere the composition of a future vaccine is formulated towards the end of the winter season (i.e. in February) so that the summer season is used for the production of vaccine for the following winter. The new strains may thus be incorporated in time to vaccinate before the following winter season in the northern hemisphere, which begins approximately in November. This would presume that little further virus evolution takes place in the tail end of the winter or in the summer (or during the winter in the lesser populated southern hemisphere).

In this respect the southern hemisphere has been somewhat disadvantaged. Up until recently, in the absence of a specific southern hemisphere formulation, influenza vaccines used here have had to conform to the formulation used for the previous winter of the northern hemisphere. So, for example, the vaccine recommendations for the 1994 season were those formulated for the 1993/94 northern hemisphere winter in February 1993; for the 1993 season those formulated for the 1992/93 northern hemisphere winter in February 1992, and so on. In many years the strains that have circulated in South Africa have corresponded almost exactly to those of the northern hemisphere vaccine formulation. However, in a number of other years the remnant of the winter season, after the February formulation meeting, as well as the following winter season in the southern hemisphere, has given the virus adequate time to mutate sufficiently to cause a significant antigenic drift and thus give rise to a new strain for which the previous strains in the vaccine would be less protective. For example, in 1993, the H₃N₂ component of the vaccine was an A/Beijing/353/89-like strain while in that year the A/Beijing/32/92 (H₃N₂) strain first appeared in the southern hemisphere (an was then

subsequently incorporated into the 1994 vaccine). The 1995 southern hemisphere formulation differed from the preceding 1994/95 northern hemisphere recommendation while 1996 and 1997 followed that of the northern hemisphere.

e) **HOW IMPORTANT IS THE MATCH BETWEEN THE VACCINE AND THE CIRCULATING VIRUS STRAIN?**

Laboratory tests for the antigenic characterization of viruses will usually demonstrate that antibodies made in ferrets will have some protective ability in the HI test against mismatched strains, but to a considerably lower level than against the same strain. In man it has been observed that with increasing age there is a progressive broadening of immunity to influenza virus strains. Exposure to natural infection as well as to vaccines rekindles the immune response to previous strains that the individual has been exposed to. Thus vaccination has two effects, that of inducing a specific immune response to a particular vaccine strain as well as stimulating an immune response to past strains. Immunity to past strains would probably, as in the case of the ferret, produce some low level immunity depending on how related the past strain is to the present strain. Thus, the older the strain is, the less antigenically related it is likely to be and the less protective the immune response would be to the currently circulating strain. It is for this reason that vaccine recommendations have laid great emphasis on the fact that vaccines should be closely matched to circulating strains.

The additional advantage of the southern hemisphere formulation which has now come about, i.e. incorporating strains into the vaccine which more closely match those circulating in the population, should significantly increase the protective efficacy of the vaccine. Vaccine formulations will be decided on by the WHO southern hemisphere reference centre in Melbourne, Australia, networking with the NIV, towards the end of September of each year. These strains would then be incorporated into a southern hemisphere flu vaccine to be ready by February or March before the following winter season.

3. INFLUENZA - THE DISEASE

a) **CLINICAL PRESENTATIONS**

Clinically there are 3 essential ways that influenza disease can present:-

- i) **An upper respiratory tract infection (URTI):** Where the disease can resemble, or be clinically identical to the common

cold or the mild URTI syndromes due to a whole host of respiratory pathogens.

- ii) **Typical influenza illness:** This is characterized by a sudden onset of fever and muscle pains, sore throat and dry hacking cough often with substernal pain. Typical influenza, unlike other URTIs is often marked by severe malaise and weakness and this debility may persist for a week or more.
- iii) **Pneumonia:** Pneumonia may be directly due to influenza virus infection or it may be a secondary bacterial pneumonia. Pneumonia may occur in immunologically competent individuals but is more severe and is the usual cause of death from influenza in the elderly and in patients debilitated by underlying chronic medical conditions.

b) COMMON COLD VERSUS INFLUENZA

Because influenza virus can be one of a large number of viruses which cause the common cold, there is often confusion regarding the efficacy of influenza vaccines. The vaccine will only protect against influenza virus infection and **not** URTI or the common cold which, in a winter season, will occur as frequently in vaccinated as in non-vaccinated persons. The vaccinated individual, however, will be protected from the more typical influenza disease with its debilitating illness which can result in absenteeism ranging from 3 to 7 days. It will also protect against the more serious complication of lower respiratory tract infections such as pneumonia and bronchitis which are not complications of the common cold or the milder URTIs.

c) COMPLICATIONS OF INFLUENZA

In addition to the direct and more visible effects, influenza is also responsible for the following complications:-

- , **Myocarditis** - may occur in healthy young individuals and not infrequently in athletes following on vigorous exercise. Strenuous training and participation in sport should be avoided during a bout of influenza. Sportsmen and athletes should therefore be vaccinated annually against influenza.
- , **Encephalitis** - post-infectious demyelinating encephalitis is a rare but potentially serious complication of influenza.
- , **Myositis** - severe focal inflammation of muscle with damage and destruction of muscle tissue is a rare complication occurring

mainly in children.

Reye's syndrome - fatty infiltration of the liver and encephalopathy is a serious complication occurring in children on aspirin therapy.

Triggering of other diseases - the role of influenza virus infection as a trigger for other diseases such as meningitis, otitis media and sinusitis is very much undervalued. A number of epidemiological studies have demonstrated seasonal increases in the incidence of a number of these conditions coinciding with influenza outbreaks.

4. THE COST OF INFLUENZA

a) HUMAN IMPACT OF INFLUENZA

Influenza is one of the major causes of debilitating illness and premature death, particularly in individuals over the age of 65 and those with chronic underlying illnesses. In the USA influenza is associated with 10 000 to 40 000 deaths annually. The toll is even higher in years of severe epidemic activity, for example in 1989/90 influenza caused 55 000 deaths in the USA (and 26 000 in the UK). Excess hospitalizations during influenza outbreaks are well over 150,000 in the USA alone in addition to the millions of days of debilitating illness.

b) FINANCIAL COSTS - USA

Influenza is estimated to cost the USA over \$12 billion annually in direct and indirect costs. Medicare reimbursement for excess hospitalizations during influenza outbreaks range from \$750 to \$1 billion. To this must also be added the millions of dollars of pharmaceutical products consumed and visits to doctors and day clinics as well as the millions of working days lost to the economy as a result of absenteeism.

c) FINANCIAL COSTS - SOUTH AFRICA

Data on the economic impact of influenza in South Africa are scanty. A recent study conducted in a large parastatal organization employing 40 000 individuals showed that the total winter-related cost for 1995 was estimated to be R13.5 million of which it is estimated that approximately 40% was related to influenza. The study also focussed on the influenza related medical and pharmaceutical costs within the medical aid industry. For 1995 these costs were estimated to be R354 million.

5. INFLUENZA VACCINES

a) TYPES OF VACCINES

Influenza vaccines in present use are inactivated vaccines prepared by growing up seed virus corresponding to the recommended strains in fertilized chicken eggs and egg culture. The virus is then chemically inactivated and the product is extensively purified to remove any contaminating egg protein and other culture debris. Three kinds of vaccines are then prepared.:-

- i) **Whole virus vaccine:** This vaccine is composed of the whole virus particle including the H and N proteins.
- ii) **Split-product vaccine:** Here the envelope is digested by detergents or organic solvents and the soluble H and N proteins together with internal proteins are freed from the whole virus particle and then used as the vaccine.
- iii) **Subunit vaccine:** In this product the H and N proteins are extensively purified by procedures such as zonal centrifugation so that the vaccine consists essentially of these proteins only. These vaccines are also referred to as **purified surface antigen vaccines**.

Splitting of the envelope to extract the H and N proteins was originally conceived in order to reduce the side-effects of the vaccine which are due, in large measure, to the envelope lipid. However, in doing so, earlier split-product and subunit vaccines displayed considerably reduced immunogenicity (as the adjuvant effect of the lipid envelope was removed). However, modern split-product and subunit vaccines are adsorbed onto adjuvants such as aluminium phosphate or aluminium hydroxide and their immunogenicity is comparable to that of the whole virus product. In similar vein, modern whole virus vaccines are extensively purified so that the incidence of side-effects is not significantly different to subunit or split-product vaccines. In adults all three vaccines can be used inter-changeably and there is no advantage between them. In children, there is a preference for the split-product or subunit vaccines.

b) ADMINISTRATION OF INFLUENZA VACCINES

- i) **Route of administration:** Influenza vaccine should be inoculated by intramuscular injection in the upper deltoid region of the arm in children and adults and the anterolateral aspect of

the thigh in the rare instances where young infants need to be immunized. Subcutaneous administration of the vaccine is less desirable than intramuscular (even though some package inserts of commercial vaccine may indicate it as an alternative route of administration). Seroconversion rates have been shown to be lower with subcutaneous injection and side-effects, particularly soreness of the arm, are more frequent. The vaccine should never be given intradermally or into the gluteal region.

- ii) **Timing and schedule:** The protective effects of influenza vaccine coincide with the development of antibodies some 14 days after inoculation. Influenza vaccine should therefore be administered well before the winter season. Influenza viruses usually make their appearance towards the latter part of May and early June. Vaccine should ideally be administered during April and early May.

N.B. It is important to note that there is no cut-off date for influenza vaccination. Clearly, it is preferable to vaccinate **before** the onset of winter to ensure timeous protection. Influenza outbreaks, however, not infrequently commence later in the year, or dominant strains may well make their appearance relatively late in the season. It is therefore never too late to give influenza vaccine accepting, however, that it does take two weeks for protection to come into effect.

Influenza vaccine is administered as a single dose except in children. (Children under the age of 3 years should receive half the adult dose, as a single dose if they have been vaccinated previously or 2 doses separated a month apart if it is the first time they are being vaccinated. Between 3 and 9 years of age, children should receive the adult dose as a single dose or two doses, a month apart, also depending on whether it is a first-time or repeat vaccination. Above the age of 9 years children would require a single adult dose.)

c) **SIDE-EFFECTS**

Side-effects of influenza vaccine are rare and usually trivial. Significant side-effects occur in less than 5% of vaccine recipients. They do, however, occur more frequently and with greater severity in elderly individuals, especially the frail elderly, as well as

patients debilitated by chronic illnesses - precisely those individuals who are at high risk of influenza and its complications, and the most important candidates for routine vaccination.

The most frequent side-effects are discomfort, inflammation and induration at the site of injection. (This may be accompanied by low grade fever, myalgia, headache and lassitude.) Rarely, a debilitating illness may occur in some elderly persons as described above.

d) PRECAUTIONS AND CONTRAINDICATIONS

Influenza vaccine is contraindicated in the following persons:-

- i) **Hypersensitivity to egg protein:** Even though modern vaccines are so highly purified that only minute traces of egg protein may remain behind as contaminants, individuals with a history of severe egg hypersensitivity should not receive influenza vaccine.
- ii) **Previous history of severe adverse reactions:** Those individuals (mainly elderly) who have previously displayed severe adverse reactions to influenza vaccination should be carefully evaluated. A different vaccine could be tried, for example, changing from a whole virus vaccine to a split-product or subunit vaccine, or the dose could be halved and administered on two separate occasions separated a month apart. Unfortunately they are often precisely the persons who are at highest risk of influenza and a careful weighing of the balance of risks must be considered when coming to a decision to withhold vaccine.
- iii) **Pregnancy:** It is preferable not to administer influenza vaccine during the first trimester of pregnancy purely as a safety precaution - there is no evidence whatsoever of any risk to the foetus. In situations where a high risk pregnant mother would be exposed to influenza, the balance of risks again must be evaluated and the possibility of postponing vaccination to the second trimester should be considered.

The vaccine is not contraindicated in immunosuppressed individuals. It is, in fact, indicated in these patients. The efficacy may be somewhat reduced and it may be advisable to administer two doses separated a month apart.

e) EFFICACY OF INFLUENZA VACCINATION**i) The specific efficacy** of influenza vaccine depends on three factors:-

, **Age:** In healthy young adults the vaccine is up to 90% effective. It is somewhat less effective in the elderly (because of an aging, less efficient immune system) and in young children (because of little or no previous experience of influenza virus and therefore an absence of a boosting effect) where the efficacy may drop to about 70%.

, **Immune status:** In immunosuppressed patients and patients with chronic metabolic disorders, especially chronic renal disease, the efficacy is reduced, often to 50% or lower.

, **Antigenic match of the vaccine:** The efficacy is markedly affected by the antigenic match of the strains incorporated into the vaccine and those circulating in the population. It is therefore most important that the vaccine which is used should contain the specific strains recommended for that year and for the southern hemisphere.

ii) The protective efficacy of influenza vaccine in preventing disease has been demonstrated in many investigations in a variety of subjects throughout the world.

, **Mortality:** The overall reduction in mortality from influenza as a result of vaccination has been shown to be about 50%. Repeated annual vaccination is, however, far more effective in reducing mortality than first-time vaccination - it was only 9% in first-time vaccine recipients compared to 75% in those vaccinated previously. Vaccination was effective in preventing 27-30% of deaths due to all causes.

, **Hospitalization:** Vaccination reduced hospitalization for pneumonia due to all causes by 31-45% in Medicare patients, and 48-50% in a large HMO in the USA. Hospitalization for congested cardiac failure was reduced by 37%.

, **All acute and chronic respiratory illness** in an

elderly population was reduced by 27-39%.

Healthy young working adults: There were 25% fewer episodes of all upper respiratory illnesses and 43% fewer days of sick leave. These figures do represent a considerable under-estimate of the efficacy of influenza vaccination because many other causes of respiratory illness and influenza-like illnesses are not due to influenza virus and are therefore not specifically prevented by influenza vaccine.

f) COST-EFFECTIVENESS OF INFLUENZA VACCINATION

- i) **Medicare influenza demonstration:** Perhaps the most rigorous investigation of the cost-effectiveness of influenza vaccination was the 4-year US Congress mandated Medicare influenza demonstration. In 1988 the Health Care Financing Administration and the CDC in the USA conducted a 4-year demonstration project to evaluate the cost-effectiveness of providing influenza vaccine to Medicare beneficiaries. This investigation found that Medicare reimbursement for excess hospitalization ranged from \$750 million to \$1 billion per influenza epidemic. Various aspects of cost benefit were convincingly demonstrated, for example the cost of influenza vaccination was calculated at \$145 per year of life gained which is substantially lower than other preventative interventions (for example the estimated cost of cervical cancer screening was \$1 600 to \$2 900 per year of life gained). Because of these favourable findings, in May 1993 influenza vaccination was made a covered Medicare benefit.
- ii) **Cost-savings of vaccination:** The cost-savings of influenza vaccination have varied markedly depending on the population being evaluated and the method of vaccine delivery (i.e. mass vaccination programmes are considerably more cost-effective; vaccination in the elderly is substantially more cost-saving). The lowest estimated cost-saving amongst Medicare recipients in 1993 was \$2.32 per beneficiary per vaccine. The estimated savings amongst healthy working adults in an HMO was found to be \$46,85 per year in 1995, and in elderly persons in the same HMO the direct cost-savings were found to be \$117 per

- year.
- iii) **Influenza vaccine costs compared to other preventative programmes:** Influenza is the most cost-effective of all medical preventative interventions in adults (see Table).
- iv) **Economic costs saved:** The US Office of Technology Assessment estimated over a seven year period that influenza accounted for 15 million days of work lost per year - equivalent to approximately \$764 million of lost productivity per year. On the other hand, vaccine administration of 150 million doses over a seven year period cost \$808 million and this prevented 5 million days of work lost. The nett saving for vaccination was calculated at \$253 million in lost productivity. The true economic savings are, in fact, considerably more as costs of hospitalization, drug treatment, physicians visits etc., are not taken into account in these estimates.

TABLE: COMPARATIVE COSTS OF MEDICAL INTERVENTIONS

Intervention	Cost per year of life saved
Influenza vaccination	\$ 145
Cervical cancer screening	\$ 1 600 - 2 900
Counselling to stop smoking	\$ 6 463
Early AZT for HIV	\$ 6 553
Renal dialysis	\$ 46 249
Coronary artery bypass	\$113 087
Mammography screening	\$167 850

g) INDICATIONS FOR VACCINATION

i) **Medically Mandated Vaccination:**

- , **High risk groups:** These groups of individuals are well known and failure to provide vaccine to these individuals could, in very high risk patients, constitute grounds for negligence. These high risk groups include:-
- Elderly (over 65 years; younger in chronic smokers)
 - Chronic lung/heart disease patients
 - Immunosuppressed persons
 - Chronic metabolic disorders, e.g. diabetes, chronic renal failure
 - Children with the same chronic medical conditions as outlined above for adults and also children on long-term aspirin therapy

Individuals in regular contact with high risk persons: These include:-

Healthcare workers

Personnel in institutions for the aged, convalescent homes and institutions for the chronically ill

Household contacts of high risk individuals, including children

ii) **Cost-Benefit Immunization:**

Because of the extensive absenteeism due to influenza in the workplace during the winter season and the economic costs thereof, vaccination of the workforce is not only a considerable employee benefit, it is also highly cost-beneficial.

The economic benefit of immunization does, of course, extend well beyond employee vaccination. The cost of 3-7 days of absenteeism to a self-employed person would be many orders of magnitude greater than the cost of influenza vaccine.

iii) **Sportsmen and athletes** constitute a special group of individuals where influenza vaccination would not only be an important option for reducing the risk of absenteeism for training and participation in sport, but would also protect against the very serious risk of myocarditis which is an ever-present hazard to sportsmen.

iv) **Personal protection:** Any individuals wishing to protect themselves from an uncomfortable and debilitating illness which results in absence from work and earning an income for some 3-7 days, should avail themselves of a safe and effective and relatively cheap protective vaccine.

h) SPECIAL ISSUES REGARDING INFLUENZA IMMUNIZATION

i) **Travellers and influenza vaccination:** The problem arises frequently of high-risk persons travelling from South Africa to countries in the northern hemisphere during their winter season. Advice is sought not only from persons in high-risk categories but also by businessmen fearful of the consequences of a bout of influenza during an overseas business trip. The difficulty is that influenza vaccines are frequently unavailable during the South African summer and the formulation is, in most years,

different to that used for the northern hemisphere. High-risk persons should be vaccinated with strains recommended for the current northern hemisphere season as soon as possible after arriving at their northern hemisphere destination, bearing in mind that protection would only commence after 14 days. High-risk persons should be advised to be protected during this interim period by a course of amantadine (Symmetrel®) (see above). Amantadine, however, is only protective against influenza A infection. It should be mentioned that some degree of protection against discordant strains does exist and therefore if local vaccine is available, it would be advisable to administer this before travel if the individual has not yet been vaccinated for the previous season.

- ii) **Egg hypersensitivity:** (see above). Histories of allergies to eggs are very common but they need not be a contraindication to receiving all egg-based vaccines including influenza vaccine. Influenza vaccines are highly purified and contain only minute traces of egg protein. A history of egg exposure-related rashes, or stomach upsets should not, in itself, be a contraindication to the vaccine. Only if there has been an episode of anaphylaxis or severe hypersensitivity with respiratory difficulty following egg ingestion, should influenza vaccination be contraindicated.
- iii) **Pregnancy:** (see above). Pregnancy is similarly only a relative contraindication. To date there has been no evidence whatsoever of any damage to the growing infant as a result of maternal vaccination. In principle vaccination should be delayed until the second or third trimester. However, if the mother falls into a high-risk category, the risk of not being vaccinated would outweigh the theoretical fear of damage to the infant.
- iv) **Simultaneous administration of vaccines:** Influenza and pneumococcal vaccines overlap in their target groups. They can be administered simultaneously although at different sites without increasing the side-effects of each of them. The same would apply to simultaneous administration of influenza vaccine with travel vaccines or any other vaccine which may need to be administered at the same time. In children, influenza vaccine can also be administered simultaneously with other vaccines

such as DPT.

j) REASONS FOR UNDERUTILIZATION OF INFLUENZA VACCINE

Given the ever-increasing evidence of the efficacy of influenza vaccine in preventing deaths and disability from influenza, the very impressive cost-benefit of vaccination, the safety and the relatively low cost, it is indeed remarkable how low the utilization of influenza vaccine is, and especially so in South Africa relative to the developed countries of the world (see Table). Two main misconceptions that are widespread amongst the profession and the lay public probably contribute to the underutilization of vaccine. These are, scepticism about the efficacy of the vaccine, and unreasoned fears of side-effects from the vaccine.

i) **Scepticism about vaccine efficacy:** Two factors are responsible for the scepticism:-

, **Confusion between influenza and the common cold** - Influenza vaccine is specifically effective against the influenza virus and has no protective effect against other pathogens which may cause URTI or an influenza-like illness. Anecdotal reports of URTI or flu-like illness after receiving the vaccine are frequently misconstrued as being vaccine failure, and in some cases there is even the feeling that the vaccine itself is causing influenza. (This is, of course, impossible as the vaccine is completely inactivated.) It bears reiterating that the important role of the vaccine is to prevent influenza infection only. However, it is influenza infection in particular which is the cause of serious complications, profound debility and prolonged absenteeism.

, **Apparent low cost-effectiveness in years of low epidemic activity** - Because the protective effect of the vaccine is specific to influenza, its efficacy in reducing illness-related work absenteeism is directly proportional to the extent of influenza activity in that year. This probably accounts for the wide variation of vaccine efficacy observed in both well controlled published studies as well as anecdotal reports. In years of low influenza activity where a large proportion of absenteeism is not due to influenza virus infection, the

vaccine's cost-benefit ratio may well be lower. Unfortunately there are no scientifically reliable ways of forecasting beforehand whether the forthcoming winter will bring a mild or severe epidemic and therefore vaccination is recommended for every winter season.

- ii) **Fear of side-effects:** The incidence of side-effects is significantly higher in children and the elderly, and especially in frail, debilitated persons. The overall incidence of significant side-effects is less than 5%. In placebo-controlled clinical trials the incidence of reported side-effects has, in actual fact, not been significantly higher in vaccine recipients as compared to placebo recipients. Unfortunately it is precisely those kind of individuals who need influenza vaccine the most, who are the ones who are the most likely to complain of post-vaccination side-effects, and many of these reports of severe side-effects are probably greatly exaggerated.

k) COMMON MYTHS REGARDING INFLUENZA VACCINATION

- i) **The vaccine causes influenza:** The vaccine is an inactivated or killed preparation and cannot cause any infection at all. Respiratory infections following on the vaccine are due to other organisms. Influenza vaccine protects against influenza virus only.
- ii) **The vaccine does not work as respiratory infection often follows vaccination:** (see answer in (i) above).
- iii) **Repeated annual vaccination reduces immunity by preventing natural infection:** Vaccination does not, in fact, totally prevent infection but protects against disease and complications. Individuals who have been annually vaccinated have the same repertoire of antibodies as persons who have never been vaccinated.
- iv) **Influenza vaccine can cause Guillain-Barré syndrome:** A few cases of Guillain-Barré syndrome followed on the nationwide vaccination campaign in the USA in 1976 in response to the swine influenza threat. Subsequent epidemiological studies have totally refuted this association and there has since been no documentation of any association,

either with the vaccine or natural infection.

- v) **After May it is too late to vaccinate:** it is never too late to vaccinate; immunity takes 14 days to develop and it is therefore preferable to ensure that individuals are immune before the onset of winter.

I) **INFLUENZA VACCINATION IN HIV-INFECTED PERSONS**

A significant and increasing proportion of the South African population is HIV positive, and influenza in HIV infected persons as well as influenza vaccine recommendations, as with other immuno-suppressed individuals, is an important component of preventative management in this growing population.

- i) **Influenza in HIV-infected persons:** The number and percentage of deaths due to influenza and pneumonia in adults between 25 and 45 years of age has more than doubled in large cities of the USA since the advent of the AIDS era. Furthermore, the peaks of these deaths have occurred in winter and have coincided with winter epidemics of influenza.

The contribution of influenza to HIV related mortality has, however, not been definitively elucidated. Nevertheless, a number of clinical studies have demonstrated that influenza is more severe in HIV infected persons and often runs a more prolonged course with a greater likelihood of hypoxia.

A major risk of both influenza and HIV is that *Streptococcus pneumoniae* and *Haemophilus influenzae* are serious and sometimes fatal complications and HIV infected persons who become infected with influenza are therefore particularly vulnerable to these two life-threatening bacterial infections.

A further complication of infection in HIV infected persons is that influenza pneumonia may present clinically similarly to opportunistic infections of HIV such as *Pneumocystis carinii*, engendering considerable anxiety and often costly and even invasive diagnostic procedures. The role that influenza plays in being a trigger or accessory to respiratory opportunistic diseases of HIV such as *Pneumocystis carinii* pneumonia or tuberculosis, still needs to be elucidated.

HIV infected persons clearly constitute an important risk group for influenza, and a group who need to be protected from

infection by vaccination on an annual basis.

- ii) **Efficacy of influenza vaccination in HIV infected persons:** A limited study (in 1987) of HIV infected homosexual men found that antibody responses to both influenza and pneumococcal vaccines did not differ significantly from non-HIV infected controls. However, a number of subsequent studies have shown that asymptomatic HIV infected persons did have significantly lower antibody responses, both in terms of the frequency of response as well as titres of antibodies and patients with HIV disease had a very much poorer response. Thus, in one prospective study, the antibody responses in HIV negative controls was 94-100% compared to 52-89% in asymptomatic HIV positive individuals and 13-50% in patients with AIDS or ARC. These poor responses are not unexpected, given that influenza vaccine is T-cell dependent and that there is profound suppression of T-cell (CD4) immunity in HIV. (Similar poor responses have been demonstrated with other T-cell dependent vaccines such as hepatitis B in HIV infected persons.) Attempts to remedy the poor response rate with a 2-dose (one month apart) booster schedule, however, have not been successful. Patients on zidovudine therapy, however, did have better vaccine responses.
- iii) **Vaccine utilization by HIV infected persons:** A number of investigations in the USA have revealed that even though HIV infection is an important indication for influenza vaccination, the vaccine utilization is lower than in non-HIV infected persons. Thus, in one study in Los Angeles, the overall proportion of HIV infected persons who received influenza vaccine was 28% (as against 30-40% for non-infected individuals). Patients receiving medical care at HMOs, had the highest vaccine coverage (45%) followed by public clinics (25%) and the lowest was found in private clinics (13%).
- iv) **Reasons for underutilization of influenza vaccines in HIV infected persons:**
- , The impression that influenza vaccine is ineffective in HIV infected persons.
 - , Lack of definitive information regarding the problem of influenza in HIV infected persons.

The fear that the administration of vaccine could stimulate and activate T-cells and thus enhance HIV replication. However, a number of studies have demonstrated that there is no long-lasting clinical or immunological deterioration following on influenza vaccination. At any rate T-cell activation would be significantly greater with the natural disease.

6. ANTIVIRAL CHEMOPROPHYLAXIS

a) CHEMOPROPHYLAXIS

Influenza vaccines are, by far, the most important means of preventing influenza. On occasion, however, it may be necessary to supplement vaccine prophylaxis with chemoprophylaxis using a drug amantadine (Symmetrel®) which inhibits influenza virus replication. Amantadine should be administered under the following circumstances:-

- i) In very high risk situations to subjects who may already have been vaccinated or, if not, together with influenza vaccine, for example to frail, elderly inmates of an institution before a threatening outbreak.
- ii) In an emergency situation where vaccine has been omitted in a high risk patient. As the protective effects of vaccination only commence after 14 days, amantadine can be utilized for protection in the interim.
- iii) Where vaccine is contraindicated - in persons who have a history of severe hypersensitivity to egg protein.
- iv) Where vaccine is not available or vaccines containing the correct strains are not procurable, e.g. travellers going from summer to winter season (see below).

Amantadine is given as a 100mg tablet twice daily for the duration of the epidemic (usually 6-12 weeks). Caution must be exercised with elderly patients (the dose is then 100mg daily), patients with renal diseases (the dose must be reduced according to the creatinine clearance) and patients with a history of seizures (who should be carefully monitored if amantadine is administered).

(An alternative to amantadine, rimantidine, is used in a number of countries overseas but is not yet licensed in South Africa.)

b) ANTIVIRAL CHEMOTHERAPY

- i) **Amantadine** may also be used as a therapy for influenza provided it is administered early in the course of the illness, i.e. within 48 hours after onset of influenza. Significant therapeutic responses have been demonstrated in the treatment of influenza pneumonia.
- ii) **Neuraminidase inhibitors** - antiviral drugs which inhibit the neuraminidase enzyme of the influenza virus are currently undergoing therapeutic trials and have preliminarily shown great promise in the treatment of influenza pneumonia.

SECTION IV

THE POTENTIAL IMPACT OF A MAJOR INFLUENZA PANDEMIC

1. THE EXTENT OF THE EPIDEMIC

As mentioned above, the extent and the impact of a future major pandemic cannot be predicted with any degree of certainty. Data from previous major pandemics may be of some value in contingency planning. The extent of the pandemics in the UK population for each of the major pandemics has been published:-

- , The 1918/19 pandemic affected 23% of the population
- , The 1957 Asian pandemic affected 17% of the population
- , The 1969 Hong Kong pandemic affected 8% of the population

Many circumstances have changed both in terms of social demography and behaviour as well as therapeutic capacity. For example, increased links with mainland China and rapid and extensive air transportation would probably significantly accelerate the dissemination of a new pandemic strain.

- S Greatly improved monitoring systems and early warning sentinel laboratories such as the WHO collaborating laboratories in China, may well facilitate early detection of new strains and allow for a more prompt response.
- S Greatly improved therapeutic options, especially antibiotic therapy and management of respiratory failure, would increase survival.
- S Increased density of population and increased population masses, together with closer working and recreational interaction between people could increase the dissemination of influenza virus.

The WHO recommendations for contingency planning suggest that 25% of the population should be taken as a target figure.

2. MORTALITY

It is highly unlikely that the enormous toll of life which occurred in the 1918/19 influenza outbreak would be repeated even though the aetiological agent of that pandemic could well have been a super virulent strain of influenza which could reappear in a new major pandemic. However, advances in therapeutic management of severe respiratory disease could ensure that even super virulent strains of influenza would not have the same degree of devastation as

in 1918/19. Nevertheless, the reappearance of the 1918/19 strain coupled with modern lifestyle factors which could accelerate its transmission would undoubtedly still cause very significant mortality in addition to overwhelming the limited availability of high care and intensive care facilities.

3. GENERAL PRACTICE

In the UK, it has been predicted that new general practitioner consultations would exceed 500/100 000 population in a new major pandemic. This would mean that a practice with a patient base of 10 000 would see at least 50 new patients per week.

At the peak of the 1957 pandemic general practitioners recorded seeing 80-100 cases per day, whereas in the 1969 pandemic these reached up to 1,260/100 000 population over a 2 week period.

4. HOSPITAL ADMISSIONS

In the UK at the peak of the 1957 pandemic, between 25-30 000 additional cases of acute respiratory disease were admitted to National Health Service hospitals.

5. WORK ABSENTEEISM

In the UK new sickness benefit claims totalled 2.5 million out of 17.5 million insured. In 1968/69 more than 1 million were received over a 5 month period. It was estimated that 8-10% of the insured population lost 3 or more working days during the 1957 epidemic. Healthcare staff were particularly adversely affected with 12.6 to 19.4% of nurses absent in one district and in one hospital nearly a third of nurses were absent.

SECTION V

INFLUENZA SURVEILLANCE AND EARLY WARNING OF AN IMPENDING PANDEMIC IN SOUTH AFRICA

1. NATIONAL SURVEILLANCE PROGRAMMES

- , The influenza laboratory of the NIV is the major surveillance site for influenza in South Africa. There are smaller sites situated in the Department of Microbiology, University of Cape Town and Department of Virology, University of Natal.
- , Both active and passive surveillance is carried out at the NIV. The active surveillance programme consists of a network of sentinel sampling sites, at present some 20 general practitioners, clinics and staff health centres which provide routine upper respiratory tract specimens from patients with acute respiratory disease for virus isolation. On average between 50 and 100 virus isolates are made annually. These isolates are antigenically typed at the NIV using reagents supplied by the WHO. The typing is then confirmed at the National Institute of Medical Research in the UK which is one of the WHO reference centres. In addition, molecular studies are carried out at the NIV to determine the polypeptide sequence of new isolates in order to determine subtle sequence changes.
- , Supplementing this acute surveillance programme is the resource of clinical material sent into the NIV for routine diagnostic purposes.
- , Virus isolation data is coupled with investigation of school and work absenteeism which is used as a rough determinant of the extent and impact of influenza.

2. INTERNATIONAL COLLABORATION

The NIV influenza laboratory is part of the international global network of some 110 reference centres throughout the world. Close ties are maintained with all centres as well as with the three WHO Collaborating Centres for Reference and Research on Influenza:-

- , The Commonwealth Serum Laboratories, Melbourne, Australia
- , National Institute for Medical Research, Mill Hill, London
- , Influenza Branch, National Centre for Infectious Diseases, CDC, Atlanta, Georgia.

Links are maintained through the internet via a programme called FluNet. All participating laboratories supply information regarding influenza activity and characteristics of virus isolates.

Three influenza collaborating laboratories have been established in China to act as international early warning sentinel laboratories to warn of the appearance of new strains of influenza virus.

SECTION VI

PRE-PANDEMIC PLANNING

1. PANDEMIC INFLUENZA CONTINGENCY COMMITTEE

A Contingency Committee would need to be established in the future and it would need to meet on a regular basis to ensure that there is a working relationship in the event of a major pandemic. This committee may need to meet approximately once a year in the pre-pandemic phase to review the annual state of the world influenza report and to review the vaccine formulation recommendations for that year. A suggested composition of such a committee would include the following:-

- , Influenza expertise from the NIV - virology and epidemiology
- , Department of Health - Director of Communicable Diseases
 - Vaccine procurement
 - Registrar of Medicines
 - Planning and logistics
 - Media Liaison
- , Representatives from vaccine manufacturers
- , Local Health Authorities

2. ROUTINE ANNUAL INFLUENZA VACCINATION PROGRAMMES

It has been widely suggested that annual influenza vaccination programmes should form a key part of pre-pandemic preparedness. The value and cost-effectiveness of annual influenza vaccination has been discussed in detail in Section III (above). The additional advantages of annual influenza vaccination programmes with respect to pandemic planning are:-

- , They sensitize the public to the value of influenza vaccination and facilitate public acceptance of the influenza vaccine, and create a perception that influenza is indeed a vaccine-preventable disease along with other vaccine-preventable diseases. This would expedite the delivery of the vaccine in the event of a major pandemic where rapid mass vaccination for adults would be required.
- , Routine annual influenza vaccination programmes would facilitate and expedite the acquiring, handling, distribution and administration of influenza vaccines by both central and local governmental authorities. The massive demand for extensive mass vaccination of adults which

would be the necessary response to a major pandemic would be greatly streamlined.

, It would improve links with vaccine suppliers on whom the country would depend for large supplies of new vaccines which would be severely restricted on a global scale in the event of a major pandemic.

SECTION VII

CONTINGENCY PLANNING DURING A MAJOR PANDEMIC

One of the tasks of the Pandemic Influenza Contingency Committee would be to prepare a contingency plan in the event of a major influenza pandemic. However, there are some general guidelines for the preparation of such a plan.

1. RECOGNITION OF THE LIMIT OF VACCINE SUPPLY

It is clear that vaccine supplies to the country would be limited in the event of a major global pandemic as there is a ceiling for vaccine production worldwide. No figures have yet been published of what the maximum output of vaccine production would be on a global scale in the event of the advent of a new subtype of influenza virus. However, the following factors would impose severe restrictions on the total amount of vaccine which could be produced:-

- , Large scale vaccine production is still dependent upon fertilized eggs for culture of virus and there would be a limit to the provision of suitable pathogen-free eggs of the requisite age.
- , Production of a vaccine seed strain would depend on creating a reassortant of a high growth donor strain with the new human influenza subtype. Precious time would go by before a suitable reassortant strain is created and established.
- , South Africa would need to compete with major users of vaccine in the northern hemisphere and because of the limited amount of vaccine which would be produced this would leave countries such as South Africa in a particularly vulnerable position.

2. PRIORITIZATION OF GROUPS FOR VACCINATION

Realizing the limitations in vaccine supply, the committee would need to create a priority list for groups to receive vaccine. This priority list would need to be drawn up by the committee after careful study of all the epidemiological factors relating to that particular new subtype of the virus and its epidemiological expression. In general terms, vaccination of key personnel needed to maintain emergency services may need to take precedence over the traditional high-risk groups. The following is a provisional and tentative list of groups of individuals in order of priority:-

- a) Healthcare personnel including staff of institutions for the elderly and infirm.
- b) Fire, police, security personnel, communications and other identified categories of personnel who provide essential services which cannot afford to be dislocated by widespread illness.
- c) High-risk individuals, e.g. those with chronic lung and heart disease, immunosuppressed persons, persons with chronic metabolic disorders such as diabetes and chronic renal failure.
- d) Residents of long-stay facilities, e.g. residential homes and convalescent homes.
- e) All persons over 75 years of age, then over 65 years of age.
- f) Women in the last trimester of pregnancy.
- g) Household contacts of high-risk persons.
- h) Age groups which on close investigation of the unfolding epidemic may be indicated as being particularly susceptible.

3. ESTIMATION OF NUMBERS FOR EACH CATEGORY

Once a priority list of groups to be vaccinated has been established, the committee would need to determine the numbers within each group. This would then enable plans to be drawn up to distribute available vaccine to the relevant groups on a priority basis. It would also allow for a system to be developed for the distribution of vaccine to the relevant priority groups.

4. ACQUISITION AND DISTRIBUTION OF VACCINE

Based on the estimated requirements of vaccine, supplies would need to be procured, stored and distributed.

5. ORGANIZATION OF VACCINATION

Contingency plans would need to be drawn up for vaccination clinics to urgently vaccinate relevant groups according to the priority list.

6. ANTIVIRAL DRUGS

Amantadine is very seldom used in South Africa for prophylaxis or treatment of influenza. In the event of a pandemic very much greater use of this drug would be required, especially for urgent prophylaxis of high-risk persons who have not been timeously vaccinated. As with vaccines, there will be a vast global demand for this agent and the vulnerability of South Africa vis-a-vis the northern hemisphere will be a major consideration.

7. TREATMENT

Contingency plans will need to take account of the fact that there may well be a dramatic increase in the numbers of patients to primary, secondary and tertiary healthcare facilities. Plans may need to be cognisant of the possible need to recruit temporary auxiliary healthcare workers, e.g. retired personnel, to help cope. There may well be potential for shortages in secondary treatment modalities, for example antibiotics, antipyretics, cough mixtures, etc. Hospitals may need to have contingency plans to suspend the admission of non-urgent cases and even mortuary and undertaking personnel may need to be drawn into contingency plans.

8. MEDIA LIAISON

An important component of contingency planning is the provision of a suitable capacity for disseminating information to the healthcare professions as well as the lay public to allay consternation and panic, to minimise factors which could aid in the transmission of influenza and to expedite vaccination programmes.

SECTION VIII

CONCLUSIONS AND RECOMMENDATIONS

1. The threat of a major pandemic of influenza due to antigenic shift and the emergence of a new subtype of human influenza virus is a very real one and if and when it does occur could have a potentially serious effect on the health of the nation.
2. There are, unfortunately, no scientific tools available to be able to predict when such a pandemic will arise, from where it will be initiated, along what routes it will spread, how rapidly it will spread, what the antigenic characteristics of the virus will be, the impact that it will have and what age groups it will predominantly affect.
3. Contingency plans will need to be drawn up as soon as the "blueprint plan" is received from the WHO influenza pandemic task force. These will include the establishment of a pandemic planning committee to draw up contingency plans. This "blueprint plan" is expected towards the end of 1997.
4. At this stage an interim pandemic planning committee should be constituted to take responsibility for drawing up a definitive pandemic preparedness plan once the WHO guidelines are released.
5. The South African contingency plan will need to define and prioritize groups to be vaccinated and then to determine what the numbers of individuals would be within each of the groups.
6. Vaccines will need to be sourced and contractual commitments for the supply of the requisite number of doses would need to be instituted.
7. Similar sourcing of antiviral agents such as amantadine will also be needed.
8. Contingency plans will need to include provision for greater demands on hospital and ancillary services as well as a special facility to disseminate information to the healthcare professions and the media.

9. Annual influenza vaccination programmes form an essential component of pandemic planning and these programmes need to be developed and expanded on in South Africa, which at present grossly underutilizes influenza vaccines.
10. Training programmes will need to be established with respect to pandemic preparedness.