DISCUSSION PAPER

# Treatment of influenza in interpandemic periods

## INTRODUCTION

Annual influenza epidemics cause significant illness and death each year in Australia, particularly among people aged 65 and over, the very young, or those with chronic cardiac illness, respiratory illness, diabetes or an immune deficiency.[1] In fact, in an average year it is estimated that 1,500 Australians die, 20,000 - 40,000 are hospitalised and many more fall ill due to influenza.[2] In the mid 1990s the total cost of influenza to the Australian economy was estimated to be around $600 million[2] – costs which can be expected to be substantially higher now.

Annual vaccination, good personal hygiene and protecting others through staying at home when ill are regarded as the primary prevention measures for influenza. However, in the absence of these measures, or sometimes despite them, influenza infections still occur. In these situations, antiviral agents can assist in the prevention and treatment of influenza.

To date, there has been very little use of antiviral agents to treat influenza in Australia for a number of reasons. Firstly, their role and effectiveness may not yet be widely appreciated by medical practitioners. Secondly, as antiviral agents are ineffective against the other infections that may mimic the symptoms of influenza, and as access to diagnostic tests is limited, doctors may be reluctant to prescribe when they are unsure whether they will be of benefit. Furthermore, treatment has to be commenced within 48 hours of onset of influenza symptoms, and patients may not visit their doctor early enough.

The Influenza Specialist Group (ISG) is an Australian network of healthcare professionals aiming to reduce the burden that influenza causes in Australia. While strongly advocating the use of influenza vaccination in line with the National Health and Medical Research Council's guidelines, the ISG is working to establish standardised, evidence-based recommendations for prescribing antivirals. In order to do that, it is important that the potential value of these antivirals is considered, and guidance is provided for their appropriate use.

In support of this aim, the ISG strives to ensure that:

1. Antivirals are used where they have the greatest benefit;
2. Antivirals are used responsibly to minimise the risk of emergence of drug resistance;
3. There is adequate availability of antivirals when required, including stockpiling for pandemic use. The World Health Organization (WHO) has indicated that improved public and professional familiarity with vaccines and antivirals, as well as increased production during interpandemic periods, will improve the level of preparedness in the face of a pandemic.[3]

## INFLUENZA: THE DISEASE

The incubation period for influenza is usually 2-3 days, but in some cases it can be up to a week. Infection is usually confined to the upper respiratory tract, and initially manifests as a headache and sore throat. Myalgia and fever begin shortly after and are usually more pronounced with influenza than with other respiratory virus infections. A cough is also common and may be protracted, and the lethargy associated with influenza may persist for weeks following infection. With influenza, even healthy young people may be incapacitated for several days and not return to full health for 2-3 weeks.

Complications such as otitis media and sinusitis are not uncommon, especially in children. More serious illness resulting in hospitalisation occurs in 0.1-2% of patients, with the greatest burden being in the elderly, the very young and those with underlying chronic illnesses.[4] The most common serious complication is pneumonia, which can be due to the virus itself or, more often, a secondary bacterial infection. Other serious complications which are less common include myocarditis, pericarditis, encephalopathy, rhabdomyolysis and Reye's syndrome. In the case of those with underlying chronic illness, much of the morbidity and mortality due to influenza is caused by exacerbation of underlying cardiac, respiratory and endocrine disorders.

## AVAILABLE ANTIVIRAL TREATMENTS

The first antiviral treatments for influenza were the adamantane derivatives, such as amantadine and these are effective against influenza A, but not influenza B. However, resistant strains emerge rapidly during treatment, and are both fully virulent and transmissible. Recently, a dramatic increase in adamantane resistance has been found among circulating influenza A(H3) viruses.[5] Thus in January 2006, the Center for Disease Control and Prevention (CDC) recommended that these drugs should not be used for the treatment or prevention of influenza A in the USA for the remainder of that northern hemisphere influenza season.[6] As the adamantane derivatives are not recommended for the treatment of influenza and are currently not preferred for prophylaxis they will not be discussed further in this document. Further details can be found in relevant review articles.[6]

The newer neuraminidase inhibitors (NIs) act by blocking the neuraminidase enzyme of influenza viruses, thereby interfering with the release of the virus from the infected cell. They have proven to be useful in the treatment and prevention of both influenza A and B, and appear to be active against all known types and subtypes of influenza. Two treatments are currently available: zanamivir, (Relenza®) and oseltamivir (Tamiflu®).

Zanamivir is supplied as a fine powder that is administered using an inhaler device and reaches very high concentrations in the lung. With zanamivir, antiviral activity begins about 10 minutes after administration but there is no significant systemic activity.[7] Oseltamivir is administered orally and reaches high concentrations throughout the body, including the lungs. Effective levels are achieved after 30 minutes and reaches near maximal concentration after 2-3 hours.[8]

| | Zanamavir | Oseltamivir |
|---|---|---|
| Shorten illness | 1-3 days | 1-3 days |
| Reduce viral shedding | 40-60% | 50-70% |
| Reduce fever | 1-2 days | 0.5-2 days |
| Reduce complications | 60-70% | 60-70% |
| Reduce pneumonia | No data | 80-90% |
| Prevention of infection | 50-70% | 50-70% |
| Prevention of influenza illness | 80-90% | 80-90% |

Source: Jefferson 2006

**Table 1: Summary of the treatment effects against influenza associated with the two NIs available in Australia**

While usage and access to NIs has historically been limited in Australia, the ISG understands that manufacturers are providing significant doses of zanamivir and oseltamivir for future influenza seasons, enabling wider usage of the products to treat seasonal influenza.

## EVIDENCE FOR THE EFFECTIVENESS OF NI THERAPY FOR INFLUENZA

### Treatment

A number of clinical trials of zanamivir and oseltamivir in healthy adults have shown that treatment which is commenced within 48 hours of onset will shorten illness duration by 1-3 days.[9,10] One large study with oseltamivir, where treatment was commenced within 36 hours of onset, showed that it reduced duration of influenza by about one third, and reduced severity of illness by 40%.[9] Benefits are similar in children and in vaccinated elderly who may contract influenza.[9,10] The benefits of NIs are certainly dependent on the timing of administration, and commencement of treatment within the first 12 hours produces substantially greater benefit than later commencement.

Treatment with NIs has also been shown to reduce complications such as otitis media in children,[11, 12] as well as more serious outcomes including lower respiratory tract infections,[13] hospitalisations[14] and even death.[15]

Importantly, treatment of influenza with either of the NIs does not appear to affect the development of an antibody response by an infected individual.[12]

### Prophylaxis

Zanamivir and oseltamivir have both been shown to be about 80% effective prophylactically in preventing influenza in household contacts and when used for seasonal prophylaxis.[13] Oseltamivir has also been shown to be effective in the control of outbreaks in long term residential care facilities, in both vaccinated and unvaccinated residents.[4]

| Body weight (kg) | Recommended dose |
|---|---|
| ≤ 15 kg | 30 mg twice daily |
| > 15 – 23 kg | 45 mg twice daily |
| > 23 – 40 kg | 60 mg twice daily |
| > 40 kg | 75 mg twice daily |

Source: Oseltamivir PI 2005

**Table 2. Recommended oseltamivir* dosage for paediatric patients by weight**

### Diagnostic testing to guide therapeutic decisions

For NIs to have greatest benefit, decisions about commencing therapy need to be made as early as possible in the clinical course of illness. The early symptoms of influenza mimic many other respiratory infections, and thus the likelihood of the infection being influenza is dependent upon the amount of influenza activity in the community at that time. Interestingly, recent Australian surveillance data indicated that the doctor's clinical impression is also important in predicting influenza.[16]

Due to the clinical uncertainty when diagnosing influenza, there is an understandable desire for diagnostic tests that assist with this decision. Unfortunately, standard laboratory-based tests usually take 1-3 days to provide results and therefore cannot really assist in decisions about antiviral therapy. More recently, rapid point-of-care tests have become available; however, these remain relatively expensive, practitioners may not be able to access them and they are far from ideal. Where such tests are used a positive result is generally a reliable indicator of influenza infection. However, up to 30% of infected individuals will receive a negative result,[17] particularly in adults. Therefore, where there is a significant risk of serious disease in the patient or their contacts, antiviral therapy is still worthwhile considering.

Within this environment, it is recommended that decisions on whether to use NIs should be based on:

- Presence of influenza in the community;
- Clinical diagnosis;
- The health risks to the patient and their contacts;
- The patients' own perceptions of the impact of influenza on their lives;
- If available, point-of-care tests which can assist in that diagnosis.[18]

### Adverse effects

The NIs have very few side effects. Oseltamivir has been associated with mild nausea, vomiting and abdominal pain in around 5-10% of patients. This is usually self-limiting and can be reduced by taking the medication after food. Zanamivir may cause bronchospasm in some patients, particularly those with pre-existing lung disease. While this side effect is very uncommon, it is recommended that patients with respiratory diseases should have a bronchodilator available when using zanamivir, and discontinue use of the drug if they experience difficulties.

### Dosage

Recommended dosage for the treatment of influenza in adults

- Oseltamivir* – 75mg twice daily orally for five days;[9]
- Zanamivir – two blisters (5mg) inhaled twice daily for five days.[10]

Recommended dosage for the treatment of influenza in paediatric patients

- Oseltamivir* – children ≥1 year of age can be given oseltamivir as a 12mg/ml suspension (see Table 2 below). The shelf-life of the reconstituted solution is 10 days;[9]
- Zanamivir – children between 5-12 years of age can inhale two blisters (5mg) of zanamivir twice daily for five days.[10]

Recommended dosage for the prophylaxis of influenza in adult patients

- Oseltamivir* – 75mg once daily for at least seven days;[9]
- Zanamivir – two blisters (5mg) inhaled once daily for 10-28 days.[10]

* Note: Dosage adjustment of oseltamivir is necessary for patients with severe renal impairment (creatinine clearance < 30mL/min). Currently there are no parenteral or nebulised formulations available.

### Antiviral resistance

Resistance to NIs is rare. No viruses resistant to zanamavir have yet been isolated from immunocompetent patients after treatment,[7] and clinical trials of immunocompetent individuals over 13 years have shown oseltamivir resistance in only 0.33% of people.[19] However, the WHO estimates a higher incidence (4%) of resistance in children treated with oseltamivir.[19] This takes into account recent publications from Japan showing the presence of drug resistant viruses in as many as 18% of treated children, albeit at low levels which did not affect the clinical course of the illness.[3, 20]

It is important to note that Japan, a country that has high usage rates of oseltamivir, uses relatively low doses to treat children, which could promote the development of drug resistance.[7] At least one study outside of Japan involving children receiving recommended weight–based doses has failed to reveal any evidence of drug resistance.[14] Furthermore, results of in vitro testing suggest that resistant variants are less transmissible compared to more common strains of influenza.

A global taskforce, the Neuraminidase Inhibitor Susceptibility Network (NISN) established in 1999 continues post marketing surveillance to monitor drug resistance. After three years of post registration community surveillance the network reported that less than 1% of over 2,000 clinical samples have displayed drug resistant mutations **and to date there is no evidence of the emergence of clinically significant resistant viruses**.[14, 21]

## GUIDELINES FOR THE USE OF NIs FOR INFLUENZA TREATMENT AND PREVENTION IN THE COMMUNITY

Treatment with NIs should only be considered where there is a reasonable likelihood that the person has been exposed to the influenza virus. Therefore, NI treatment is rarely prescribed outside the local influenza season, unless the person has recently travelled to an area of influenza activity. Additionally, treatment needs to begin as early as possible after onset of illness, and if it cannot be commenced within 48 hours then NIs should not normally be used.[9, 10] However, later treatment may be worthwhile in special circumstances such as influenza pneumonia, or infection in immunosuppressed patients, but its value has not yet been proven. These cases are generally treated at a hospital in consultation with a relevant specialist.

### Treatment of patients in groups at risk of severe illness

Severe morbidity and mortality is most likely in the very young, those aged 65 years and older and those with underlying chronic respiratory, cardiac, endocrine or immunological disorders.[1] In these groups, NI treatment has the greatest potential to reduce serious illness and complications with benefits to the patient and potential reduction of health costs. Vaccination of these risk groups (except for healthy children) is an essential component of influenza prevention. However, in some instances, vaccine effectiveness might be lower than in younger healthy adults,[4] particularly if they are immunocompromised [including the very elderly (≥ 80 yrs), transplant recipients, patients with advanced cancer and/or receiving cancer chemotherapy, patients on high dose corticosteroid therapy and patients with advanced HIV]. Therefore, antiviral therapy should be considered even in vaccinated high-risk individuals with proven or strongly suspected influenza (see Figure 1).

### Treatment of young, healthy adults

For young, healthy adults NI therapy is principally of benefit in reducing the impact influenza has on work, family, travel, educational and leisure commitments. An exception is when the person has close contact with one or more high-risk individuals, and that contact cannot be avoided during the infectious period (e.g. when they have an elderly relative at home). As vaccine effectiveness is high in young healthy adults,[4] NIs are normally only considered for vaccinated individuals within this group if they have influenza confirmed by a laboratory test.

Decisions about the use of NIs in young healthy adults need to take into account all of these factors and should be a joint decision between the doctor and the patient.

Figure 1 provides an algorithm to support clinicians in identifying whether it is appropriate for NIs to be prescribed, while Figure 2 lists a number of key questions and information to help patients make informed decisions about NI usage.

### Prophylactic use

Influenza vaccination is still the primary method of influenza prevention, however NI prophylaxis can be a useful addition in some circumstances.

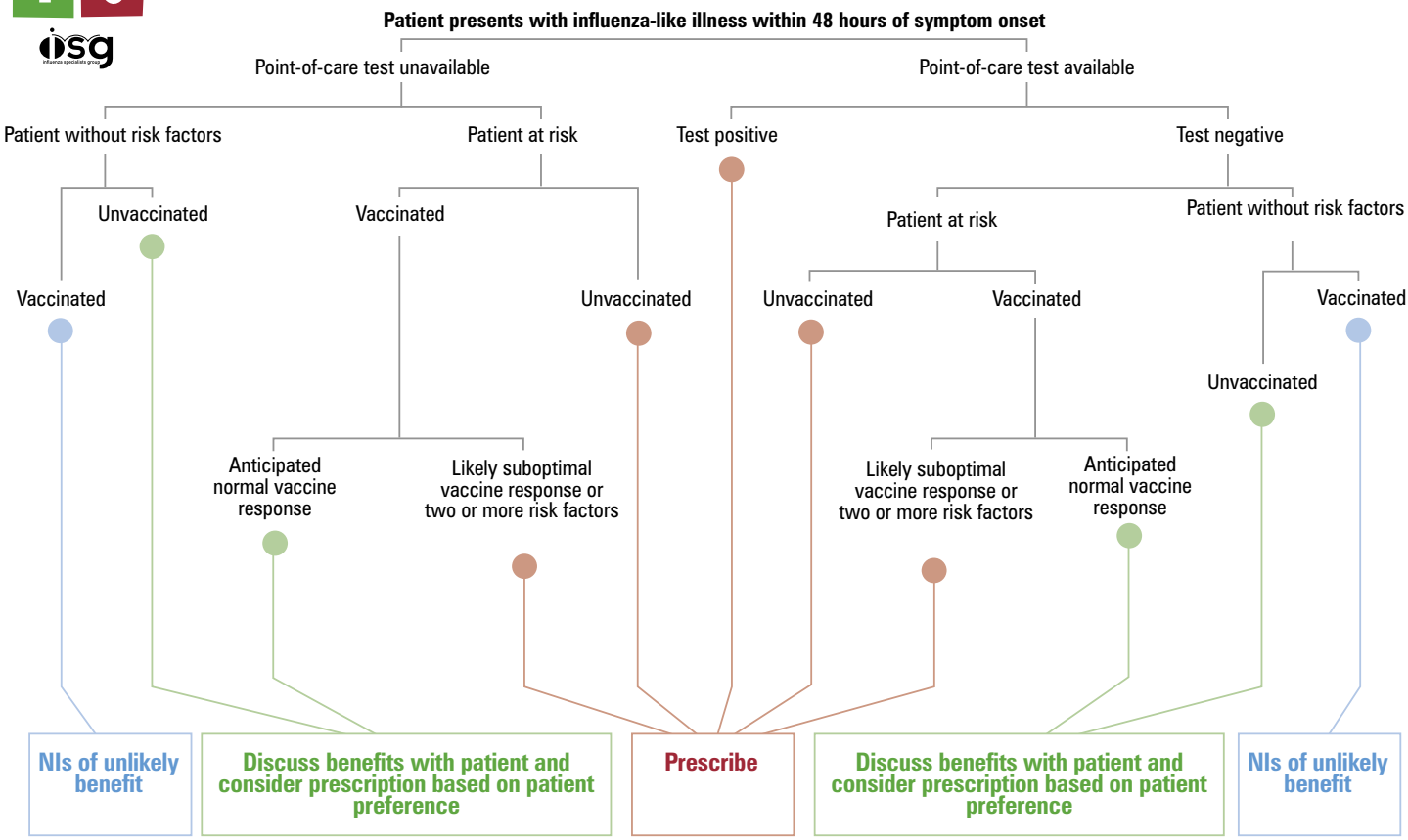
Prophylaxis for seasonal influenza may be considered for the following individuals:

- Those at high risk of severe disease and morbidity who have not been vaccinated before the commencement of the influenza season;
- Those who have contraindications to vaccination;
- Those who refuse vaccination, or who will not respond to vaccine.

Whilst prophylaxis is effective, it may require 8-12 weeks of treatment and the cost may be prohibitive for individuals.

The other use of prophylaxis is in the prevention or control of influenza outbreaks, particularly among high-risk populations in institutional settings whether they have been vaccinated or not.[4] If given to uninfected patients and staff, NIs are highly effective in interrupting outbreaks and reducing the incidence of influenza infection and illness.[22] Use in outbreaks in other settings such as boarding schools, travelling groups or within families may also be appropriate for reducing morbidity and lifestyle disruptions. In these settings, ten days of prophylaxis is usually adequate, but it may need to be extended where there is continuing or recurrent influenza activity.

## Figure 1: Algorithm for prescription of Neuraminidase Inhibitors (NIs) for influenza-like illness




# Explanatory Notes

### 1. Influenza-like illness

Influenza is generally characterised by:
• Cough • Fever • Fatigue
Which may be accompanied by:
• Rigors and chills • Myalgia • Sore throat

### 2. Onset of symptoms

NIs should not normally be used if onset of symptoms is greater than 48 hours. Later treatment may be worthwhile in special circumstances such as influenza pneumonia, or infection in immunosuppressed patients, but this has not yet been proven.

### 3. Point-of-care testing

When a point-of-care test is available, the decision to use it should be made by the treating doctor in consultation with the patient.
When point-of-care testing is used, a positive test result is of high predictive value; a negative test result has poor predictive value so should be viewed with caution. Full laboratory-based diagnostic tests such, as PCR (polymerase chain reaction) or IFA (immunofluorescence antibody), are of high predictive value for both positive and negative results, and can usually be viewed with confidence providing that appropriate samples are taken.

### 4. At-risk groups

The NHMRC defines high-risk patients as those 65 years or over, all Aboriginal and Torres Strait Islanders aged 50 years and older and children and adults with chronic conditions such as:[i]
- Diabetes.
- Cardiovascular disease.
- Renal disease.
- Immune deficiency disorders.
- Respiratory illnesses (asthma, bronchitis, emphysema etc).
- Cancer.

Other groups that are considered to require protection against infection are:[i]
- Hospital workers.
- Residents of nursing homes and other long-term care facilities.
- People that come into contact with high risk individuals.

### 5. Suboptimal vaccine response

Groups where vaccine effectiveness might be lower than in young healthy adults include:[ii]
- The "very elderly" ( ≥ 80 years of age).
- Transplant patients.
- Patients with advanced cancer and/or receiving cancer chemotherapy.
- Patients on high-dose corticosteroid therapy.
- Patients with advanced HIV.

### 6. Benefits of neuraminidase inhibitors

When treatment is commenced within 48 hours of symptom onset in healthy adults, NIs have been proven to reduce:
- Illness duration by 1-3 days.[iii,iv]
- Severity of the illness by 40%.[iii]
- Serious outcomes including lower respiratory tract infections,[v] hospitalisation[vi] and even death.[vii]

The benefits of NIs appear to be similar in the elderly and in children.[iii,iv] In addition, treatment with NIs has also been shown to reduce complications such as otitis media in children.[viii]

**To discuss the benefits of NIs with your patient, please refer to the Influenza Specialist Group 'Neuraminidase inhibitor treatment assessment'.**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Influenza Specialist Group

This document has been developed to use with the Influenza Specialist Group's 'Algorithm for prescription of NIs for influenza-like illness'. It has been developed to help GPs and patients make informed decisions about taking neuraminidase inhibitors (NIs). When making this decision two key issues must be considered:

1 Likelihood of patient having influenza.

2 Likely benefit of treatment with NIs.

Colour-coding refers to:

| |
|---|
| NIs of likely high benefit |
| NIs of potential benefit (consider other factors where possible) |
| NIs of likely low benefit |

**Influenza-like illness**
Influenza is generally characterised by:
• Cough • Fever • Fatigue

Which may be accompanied by:
• Rigors and chills • Myalgia • Sore throat

# 1 Likelihood of patient with influenza-like illness having influenza

### What time in the influenza season is it?

| | |
|---|---|
| Beginning | Low likelihood of patient having influenza |
| Middle | Substantial likelihood of patient having influenza |
| End | Low likelihood of patient having influenza |
| Outside season | It is unlikely that the person has been exposed to the influenza virus, unless the person or an immediate contact has recently travelled to an area of influenza activity |

### Has there been exposure to influenza?

| | |
|---|---|
| Not known or possible exposure | Influenza infection is possible at any time during the influenza season regardless of whether there is identifiable exposure |
| Yes, close contacts | In these circumstances it is likely that the individual has influenza |
| Yes, institutional outbreak | In these circumstances it is likely that the individual has influenza<br>Note: prophylactic NI treatment should be considered for asymptomatic institutional residents at high risk of severe consequences from influenza infection, whether or not they are vaccinated |

### Has the patient been vaccinated against influenza this season?

| | |
|---|---|
| No or unknown | In any given year, it is estimated that between 5% and 15% of the population will contract influenza[i] |
| Yes | Influenza vaccination is very effective (70-90%) in preventing influenza illness in young healthy adults.[i] However, in some cases there may be other factors which make NI treatment an important consideration:<br>• Potential severe consequences of influenza infection<br>• Patient likely to have a suboptimal vaccine response because they are immunosuppressed [including the "very elderly" (≥80 years), transplant recipients, advanced cancer, receiving cancer chemotherapy, autoimmune disease, uncontrolled diabetes] |

### What is the doctor's clinical impression of the patient's symptoms?

| | |
|---|---|
| Almost certain influenza | Where a doctor is clinically confident that the patient has influenza, they are right most of the time (56.7%)[ii] |
| Possible influenza | Where a doctor believes the influenza-like illness symptoms are possibly due to influenza, the disease is confirmed as influenza one quarter of the time (24%)[ii] |
| Unlikely influenza | Where a doctor doesn't believe the symptoms are influenza, there is generally a low likelihood of the patient having the condition |

### If a point-of-care test is available, what is the result?

| | |
|---|---|
| Positive | Most tests with positive results correctly identify infection,[3] provided there has been recent definite or possible exposure |
| Negative | A negative result cannot be considered a reliable indicator of influenza because as many as 30% of negative test results may be falsely negative.[iii] Hence caution is advised when making decisions based on this, particularly in patients at risk of serious influenza |

## 2 Likely benefit of treatment with NIs

### How long has the patient displayed symptoms of influenza-like illness?

| | |
|---|---|
| < 48 hours | NI treatment needs to begin as early as possible after onset of illness and has been shown to be of use within the first 48 hours after onset of symptoms[iv,v] |
| > 48 hours | NIs should not be used if onset of symptoms is greater than 48 hours.[vi] Later treatment may be worthwhile in special circumstances such as influenza pneumonia, or infection in immunosuppressed patients, but this has not yet been proven |

### Is the patient at high risk of influenza complications (ie, the very young, those aged 65 years and older and those with underlying chronic respiratory, cardiac, endocrine or immunological disorders)?

| | |
|---|---|
| Yes | In these groups NI treatment has the greatest potential to reduce serious illness and complications, providing obvious benefits to the patient as well as a potential reduction of health costs |
| No, but in close contact with high-risk individuals | NI treatment is important in people who have close contact with one or more high-risk individuals that cannot be avoided during the infectious period |
| No | Benefit of using NIs in young, healthy adults is mainly aimed at reducing milder morbidity and reducing the impact influenza has on work, family, travel, education and leisure commitments |


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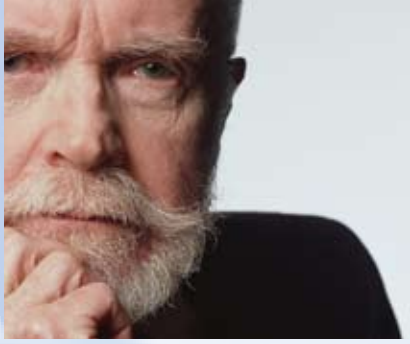

## COST AND COST-EFFECTIVENESS ISSUES

Cost-benefit analyses of influenza treatments have not been completed on a scale large enough to provide definite recommendations. However, a recent cost-effectiveness analysis found that providing NIs in the workplace to staff presenting with influenza-like illness consistently offered a cost-saving.[23] To conduct an effective cost benefit analysis, the amount of money patients spend each year on 'flu' products to relieve symptoms without having any effect on the course of the illness, direct health costs, lost productivity and other costs all need to be taken into consideration.

In the absence of large scale cost-benefit analyses, it can be considered good practice to qualify and quantify the risks and benefits of treatment, so that patients can make informed decisions about whether they want to pay for NI treatment (see Figure 2). Certainly, the benefits of antiviral treatment in a number of groups warrant a more systematic use of NIs. This is especially important for those at high risk of severe complications associated with influenza infections and in institutional settings such as hospitals or long term residential care facilities (where prophylaxis should also be considered).

## INFLUENZA SPECIALIST GROUP

The Influenza Specialist Group (ISG) consists of medical and scientific specialists and includes representatives of professional and patient groups from around the country. It cooperates with state and federal governments in educational activities regarding influenza. In conjunction with other organisations including the Australian Medical Association, WHO Collaborating Centre for Reference and Research on Influenza, Royal Australian College of General Practitioners, National Asthma Council, National Heart Foundation of Australia and Diabetes Australia it conducts an annual Influenza Awareness Program. The Program, launched in 1992, informs key audiences regarding the consequences of influenza and the importance of preventing and treating infection. The ISG receives support as educational grants from industry organisations; however the ISG, through its executive, maintains full control over all of its activities and published materials.

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