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NSW tag New South Wales Therapeutic Advisory Group Inc.

USE OF ANTIVIRALS FOR TREATMENT AND PROPHYLAXIS OF INFLUENZA IN NSW HOSPITALS AND RESIDENTIAL CARE FACILITIES

A position statement of the NSW Therapeutic Advisory Group Inc.

May 2006

SCOPE

The purpose of this position statement is to assist hospital Drug and Therapeutics Committees to develop local hospital policy in this therapeutic area.

The following clinical questions will be addressed in this paper:
a) Are antivirals recommended for treating patients with influenza-like illness in hospitals or residential care facilities during seasonal influenza outbreaks?
b) Are antivirals recommended for prophylaxis of influenza in patients in hospitals or residential care facilities during seasonal influenza outbreaks?
c) Should hospitals and/or residential care facilities hold stocks of antivirals for treatment and prophylaxis of seasonal influenza in addition to stockholding under WHO guidance for a potential influenza pandemic?

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EXECUTIVE SUMMARY

1. Antivirals can reduce severity and duration of influenza in otherwise healthy people. Neuraminidase inhibitors (NIs) – oseltamivir and zanamivir – reduce time to alleviation of all symptoms by up to 1.5 days in influenza A and B if they are given within 48 hours of symptom onset. There is no reported resistance to NIs in Australia, although resistance has been reported with some strains of influenza internationally. NIs lead to some reduction in viral shedding, but their resultant effectiveness in reducing viral transmission is unclear. Amantadine is only active against influenza A and resistance readily occurs.

2. Most trials have been conducted in otherwise healthy adults. There is insufficient evidence that antivirals prevent complications in at risk people.

3. Epidemiologic modelling suggests that targeted use of antivirals will be an important containment measure in the event of an influenza pandemic. Antivirals are currently being stockpiled due to the threat of a pandemic so supplies for other uses such as prophylaxis and treatment for seasonal influenza are constrained.

4. Existing data on influenza hospitalisations underestimate the true number of Australians hospitalised with influenza each year. Case definitions of influenza-like illness differ by state and year and there is limited value in diagnosing influenza using clinical criteria. Epidemiologic surveillance data should be taken into account and rapid point of care testing used where possible. Point of care testing has low sensitivity so negative results do not rule out influenza – but false positive results occur rarely. Interpretation of the rapid test varies according to prevalence of circulating influenza eg a negative test during influenza season could still mean the patient has influenza, while outside influenza season it is more likely the patient has another illness.

5. Influenza outbreaks in the acute hospital setting are reported infrequently and mortality appears low. Elderly people in long-term care are most at risk of complications and death during an institutional outbreak. Prompt recognition of institutional outbreaks (especially in the long-term care setting) is critical and the use of rapid testing is encouraged if antivirals are to be used effectively. The appropriate duration of influenza post-exposure chemoprophylaxis for exposed staff and residents during an outbreak is uncertain but residents will likely need to continue prophylaxis until the end of the outbreak.

6. NIs for treatment and post-exposure prophylaxis of influenza may be cost-effective in nursing home populations, although cost-effectiveness has not been formally evaluated in the Australian setting. Current evidence suggests that NIs are not cost effective in otherwise healthy adults.

7. The majority of adults present to their GP with influenza after the first two days of illness thus precluding the effective use of antivirals. This is likely to be the same situation with patients presenting to hospital emergency departments.

RECOMMENDATIONS:

1. Effective infection control measures, based on strategies to limit transmission (i.e. contact and droplet precautions), should be utilised to reduce the risk of an institutional outbreak of influenza.

2. Vaccination of at risk[i] people and healthcare workers remains the primary means of preventing seasonal influenza, in conjunction with good infection control and hygiene measures as above.

3. Amantadine should not be used for treatment or prophylaxis of influenza due to high rates of resistance.

4. Neuraminidase inhibitors should not be used for treatment or routine prophylaxis of seasonal influenza in people not at risk of complications, due to their lack of cost-effectiveness and minor clinical benefits in this population.

5. Mortality from nosocomial outbreaks among already hospitalised patients is reportedly low. Also, of those patients presenting to the emergency department with influenza, many will present after the first 48 hours of illness thus precluding the effective use of antivirals. Therefore the role for antiviral agents in treatment and post-exposure prophylaxis is limited in the acute hospital setting.

6. In the event of an institutional outbreak of seasonal influenza in the residential care setting, there is a role for antiviral agents in treatment and post-exposure prophylaxis of elderly people or other at risk people. Stock holdings in hospitals to cover these circumstances may be appropriate. Use of rapid point of care testing for influenza to guide treatment decisions at the beginning of the outbreak is recommended. The decision to use antivirals in an outbreak in the residential care setting should be guided by the local public health unit.

7. Both rapid testing and provision of an antiviral agent for a nursing home outbreak of influenza will require a rapid response procedure to be developed to ensure equity of access and consistency of approach across the State. This will require coordination between the nursing home, general practitioners, public health unit, laboratories and hospital pharmacies if the 48 hour timeline is to be met.

8. Neuraminidase inhibitors should be reserved for serious epidemics or pandemics in conjunction with other public health measures. If H5N1 influenza (or any other new pandemic strain) is suspected refer to NSW Health Department, Commonwealth Department of Health and Ageing and World Health Organization guidance.

[i] See page 9 for definition of at risk patients

BACKGROUND:
There is worldwide concern about the imminent threat of an influenza pandemic, particularly with the H5N1 avian influenza strain. The neuraminidase inhibitors (NIs) – oseltamivir (Tamiflu®) and zanamivir (Relenza®) – have been shown to reduce the severity and duration of illness due to influenza A and B during seasonal influenza epidemics and the M2 ion channel inhibitor amantadine (Symmetrel®) could also be useful in the event of a pandemic.[1] Antivirals are effective in preventing influenza and reducing the severity and duration of the illness and they have been shown to reduce viral shedding, but their resultant effectiveness in reducing viral transmission is unclear.[2-5] Epidemiologic modelling has shown targeted antiviral prophylaxis is potentially an effective measure for containing influenza until adequate quantities of vaccine are available.[6]

Supplies of oseltamivir are constrained because many countries, including Australia,[2] and the WHO are stockpiling oseltamivir in case of a potential influenza pandemic and the manufacturing process is complex and time consuming.[1] Oseltamivir is the largest component of Australia's National Medicines Stockpile (NMS), although the NMS also has supplies of zanamivir and amantadine.[2] NSW Health also has a smaller stockpile of antivirals known as the State Medical Stockpile.[7] NSW Health has provided guidance to hospitals on stockpiling oseltamivir[8] and is in the process of revising standing orders for mass administration of anti-influenza prophylaxis to defined community contacts of avian influenza (personal communication, Dr Michelle Cretikos, Biopreparedness Unit, NSW Health).

In light of this situation, there is a need to define the role of antivirals in treating or preventing influenza in hospitals in the context of individual case occurrences, seasonal epidemics and potential pandemics.

SEARCH METHODOLOGY
In preparing this statement, guideline clearinghouses and websites of guideline developers were searched using the terms "influenza" and "antivirals".

A number of searches were run in MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effectiveness using the terms:
1. (((oseltamivir or zanamivir or amantadine) and (hospital or nursing home or residential care) and influenza) not Parkinson*).
2. (exp Influenza, Human/bl, mi, mo, pa, ec, ep, th, tm, vi [Blood, Microbiology, Mortality, Pathology, Economics, Epidemiology, Therapy, Transmission, Virology] limited to English language) AND (exp Australia/ep, th [Epidemiology, Therapy])
3. (Influenza or oseltamivir or zanamivir or amantadine) and (systematic review) limited to English language

Articles were selected in the first instance if they were a guideline or systematic review/meta-analysis regarding influenza prophylaxis and/or treatment, and otherwise if they addressed the issues of managing influenza in the hospital/residential care context or the epidemiology of influenza in Australia. References lists of studies were also searched.

PHARMACOLOGY
Oseltamivir and zanamivir inhibit the viral surface enzyme neuraminidase and thus reduce virus replication[9]. Oseltamivir is currently approved in Australia for treatment of infections due to influenza A and B virus in people 1 year and older and for prophylaxis of influenza in people > 13 years. Zanamivir is approved for treatment of infections due to influenza A and B virus and prophylaxis of influenza A and B virus in healthy young adults, when there is a pandemic with a strain not included in the annual vaccine or if vaccine is unavailable[9]. Both drugs are recommended for administration within 48 hours of symptom onset.

Oseltamivir reduces the time to alleviation of all symptoms by up to 30 hours compared with patients taking placebo.[10] For zanamivir the median time to alleviation of all symptoms is 1.5 days in adults and one day in children.[4] Amantadine is usually used to treat Parkinson's disease. It only has antiviral activity against influenza A and is registered for prevention in non-immunised people or for those in whom influenza could have serious consequences.[11]

Oseltamivir, zanamivir and amantadine are not subsidised by the Pharmaceutical benefits Scheme (PBS) for either prevention or treatment of influenza and are only available on private prescription for these indications.

Recommended doses are available in the relevant product information documents.[3, 4, 9, 11]

Side effects of oseltamivir include nausea and vomiting.[3] Zanamivir, which is taken by inhalation, may rarely cause respiratory problems.[4] Refer to product information for more detailed information on the pharmacology, side effects, adverse reactions and other relevant information for oseltamivir,[3] zanamivir[4] and amantadine.[11]

Antiviral Use in Young Children

There are no data on use of antivirals in children under the age of one year and neither oseltamivir nor zanamivir is licensed for use in this age group. However, in children under one year of age with influenza, oseltamivir can be considered for treatment at a dose of 2mg/kg/day twice daily for five days (Personal Communication, Professor David Isaacs, Senior Staff Specialist in Allergy, Immunology and Infectious Diseases, Children's Hospital at Westmead). In such cases the guidance of an infectious diseases specialist is recommended.[12]

ANTIVIRAL UTILISATION

Because oseltamivir and zanamivir are not subsidised via the PBS, comprehensive information about their utilisation in the community is limited.

In the most recently available version of the Australian Statistics on Medicines, there are no data regarding oseltamivir utilisation in the Australian community[13]. Zanamivir utilisation, estimated from prescriptions dispensed at 150 community pharmacies across Australia in 2001, 2002 and 2003 was 0.005, 0.002 and 0.002 defined daily doses (DDDs[i])/1000 population/day respectively. There were 2,560 prescriptions for zanamivir in 2003, which has a DDD of 20 mg.[13]

Although Australian Statistics on Medicines does include data on amantadine utilisation, it does not specify whether the utilisation was for Parkinson's disease or influenza prophylaxis. Thus, these data are not included in this report.

There is no central repository of data on antiviral utilisation in NSW hospitals. Thus hospital utilisation of antiviral drugs for influenza is currently unknown. An informal survey of NSW TAG member hospitals shows oseltamivir and zanamivir utilisation in 17 hospitals across NSW has been low during the years 2001-2005. Figure one shows the number of packs of antivirals dispensed during 2001-2005 from these 17 hospitals.

[i] DDDs are established by the WHO Collaborating Centre for Drug Statistics Methodology and are based on the assumed average dose per day of the drug used for its main indication by adults. The DDD does not necessarily reflect the average daily dose in current Australian usage. However, it is a useful measure for comparing drug utilisation between countries and over time.

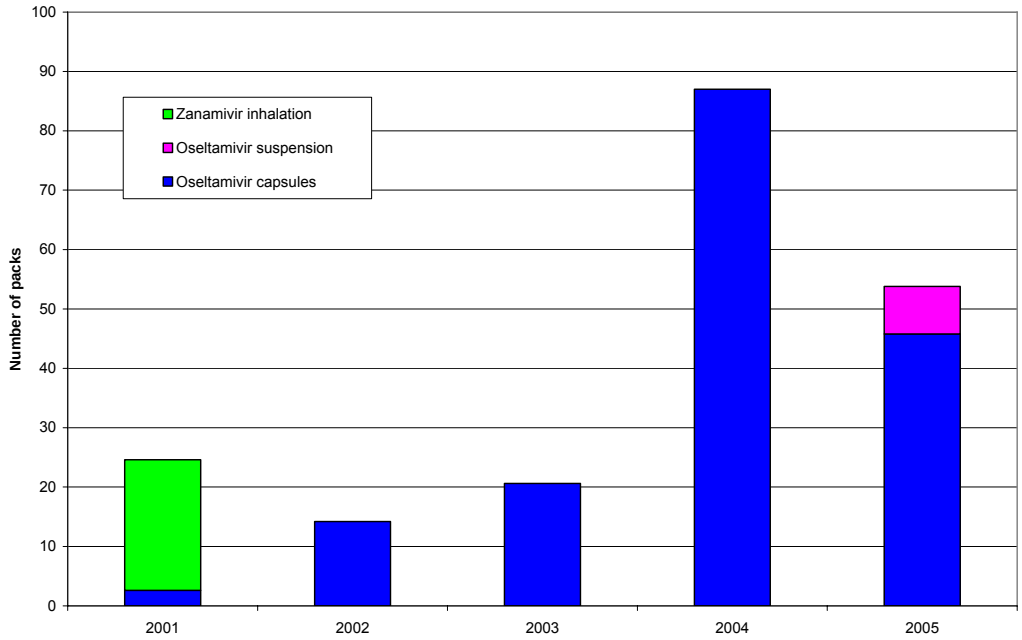

Figure 1: Packs of antivirals dispensed in NSW hospitals by year, 2001-2005

It is not known whether provision of antivirals within 48 hours of symptom onset can be achieved in the normal Australian health care setting. The barriers to this include access to a GP appointment/emergency doctor, access to rapid testing, the cost to the individual patient and a possible lack of knowledge in the community regarding the necessity to seek medical care as soon as symptoms begin.

EPIDEMIOLOGY OF INFLUENZA HOSPITALISATION

According to data from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database,[14] crude numbers of patients hospitalised with influenza across Australia have remained relatively stable between 1998/99 and 2003/04 as shown in Table 1. Age-standardised rates of influenza hospitalisation have not been calculated. However, recent research shows the incidence of hospitalisation is consistently between 2-11 times higher in young children than in adults.[15] The number of notifications of influenza in NSW to the National Notifiable Diseases Surveillance Program[16] has increased between 2002 and 2005 as shown in Table 2 (influenza first became notifiable in 2001[17]). Additionally, the number of notifications of influenza in NSW has remained lower than the national average for these years. Quarterly data from NSW Health on influenza notifications in NSW residents is presented in Figure 2. These data are likely to significantly underestimate the true rate of influenza hospitalisation as laboratory confirmed influenza is only a small proportion of all cases and reports based on clinical suspicion could vary over time and location due to different case definitions.[18] The effect of influenza on other causes of hospital admission such as cardiac and worsening respiratory disease during influenza season is difficult to assess but likely to be significant.

In NSW, there are no good data on the frequency of influenza outbreaks in hospitals or nursing homes as outbreaks of influenza are not notifiable (personal communication Dr Jeremy McAnulty, Director, Communicable Diseases Branch, NSW Department of Health).

Table 1: Crude numbers of influenza separations from Australian hospitals 1998/99-2003/04 (ICD-10-AM coding) Source: AIHW National Hospital Morbidity Database[14]

Separations –	1998-99	1999-00	2000-01	2001-02	2002-03	2003-04
Total for ICD-10-AM codes J10 and J11	5810	5182	4766	3672	4412	5424

Table 2: Notifications of influenza (laboratory confirmed) in NSW and Australia 2002-2005 Source: National Notifiable Diseases Surveillance Program[19]

	Number of notifications NSW	Number of notifications Australia	Notification rate/100,000 population NSW	Notification rate/100,000 population Australia
2002	996	3654	14.9	18.4
2003	861	3487	12.8	17.3
2004	1012	2133	14.9	10.5
2005	1419	4628	20.9	22.8

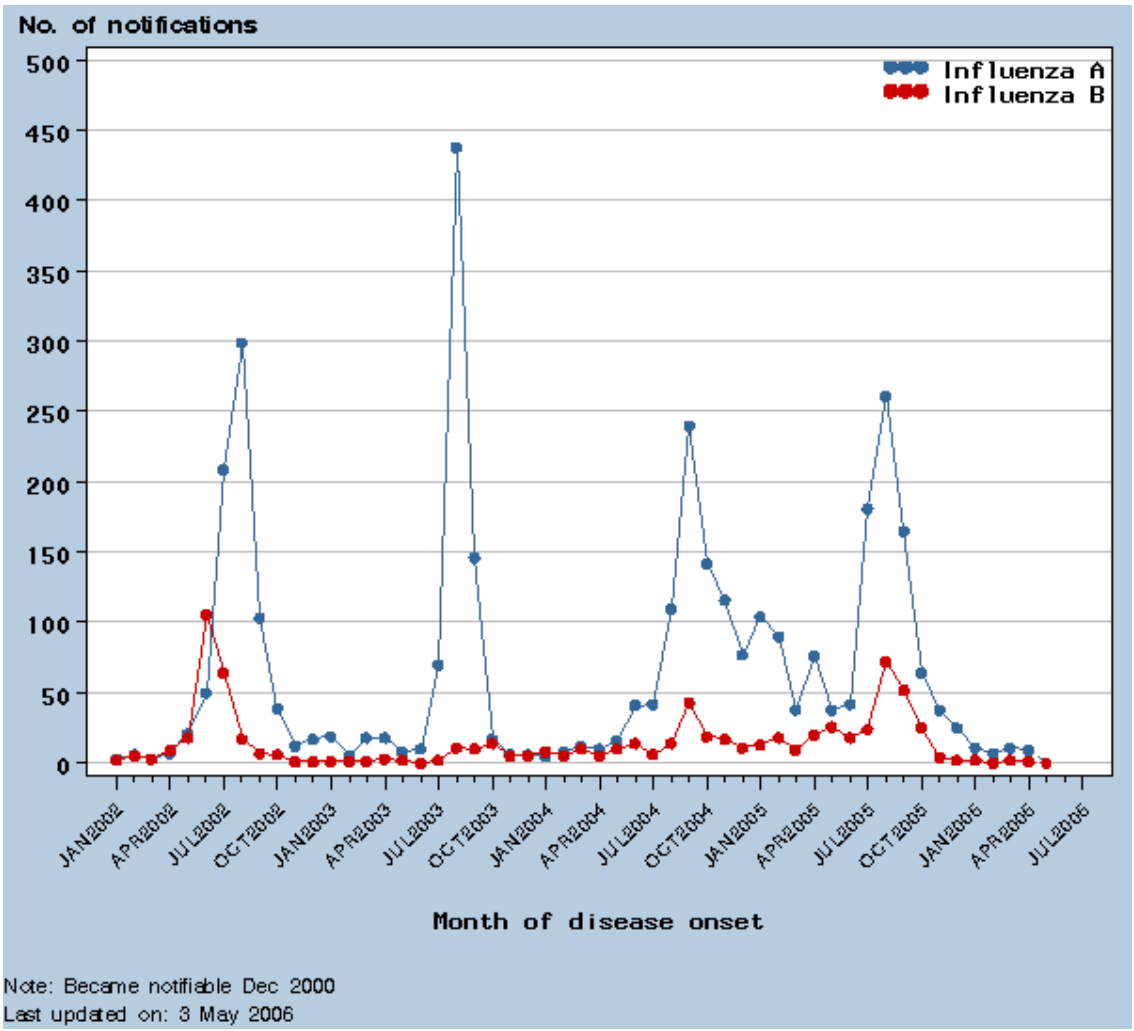

Figure 2: Influenza notifications in NSW residents, by month of disease onset. January 2002 to May 2006. Source: NSW Health[20]

DIAGNOSIS AND CASE DEFINITIONS

Australian sentinel practice schemes case definitions of influenza vary by State and year but comprise some or all of the following combinations: [18, 21, 22]

- Fever, cough, fatigue or
- Six of the following symptoms with sudden onset (<12 hours previously): cough, rigors/chills, fever, prostration and weakness, myalgia, redness of mucous membranes, influenza in close contacts
- Influenza epidemic plus four of the criteria listed above
- Viral detection or serological evidence of influenza virus infection

A systematic review of seven studies found limited value in individual signs and symptoms for diagnosing influenza.[23] A more recent systematic review found clinical findings can identify patients with an influenza-like illness but could not confirm or exclude the diagnosis of influenza. The authors recommended that clinicians also take into account whether influenza is currently circulating or use rapid diagnostic testing when treating patients with influenza-like illness.[24]

RAPID POINT OF CARE TESTING

There are four types of laboratory testing for influenza available in Australia:[25]

- Rapid point of care (POC) testing usually based on immunoassay – with a visual result within approximately 15-30 minutes
- Antigen detection using immunofluorescence (IF) – with a turnaround time of around 2-4 hours
- Nucleic acid detection using polymerase chain reaction (PCR) - with a turnaround time of around 4-5 hours
- Viral culture - with a turnaround time of around 1-4 days

Rapid POC immunoassays generally do not distinguish between influenza types A and B, although nucleic acid detection using IF may do so. The sensitivity of rapid POC immunoassay is approximately 80%, so negative results do not rule out influenza, but false positive tests are uncommon.[26] Test performance is dependant on the prevalence of influenza in the community so the diagnosis should be confirmed using IF, viral culture or PCR – especially during periods of low influenza activity.[27] A negative test during influenza season could still mean the patient has influenza while outside influenza season it is more likely the patient has another illness. In practice, access to rapid testing has enabled the prompt initiation of antiviral prophylaxis and possible outbreak control in Australia.[28]

The WHO recommends rapid POC testing should be carried out when the results will influence clinical decision-making. This may be particularly relevant at the beginning of the influenza season, in hospitals, residential care and other health care institutions. The POC test needs to be carried out within 48 hours of symptom onset to allow timely use of antiviral drugs.[27] POC testing may not differentiate between human and avian influenza (although PCR testing does), thus diagnosis of avian influenza needs to be made in combination with clinical findings and exposure history. In general, the use of rapid tests to diagnose a pandemic influenza strain is not recommended.[27] Testing for a pandemic influenza strain should be in accordance with WHO guidelines.[29]

Further discussion of advantages and disadvantages of antiviral tests can be found in Playford and Dwyer.[25]

CATEGORIES OF AUSTRALIANS "AT RISK"

In Australia, individuals who are recommended to have an annual influenza vaccination because of increased risk of influenza-related complications are: [30]

- All individuals aged 65 years and older
- Children (≥ 6 months of age) and adults with chronic cardiac conditions including cyanotic congenital heart disease, coronary artery disease and congestive heart disease
- Children (≥ 6 months of age) and adults with chronic suppurative lung disease, including bronchiectasis, cystic fibrosis and emphysema

- Children (≥ 6 months of age) and adults with chronic illnesses requiring regular medical follow-up or hospitalisation in the preceding year, including diabetes mellitus, chronic metabolic diseases, chronic renal failure, haemoglobinopathies or immunosuppression (including immunosuppression caused by drugs)
- Persons with immune deficiency, including HIV
- Residents of nursing homes and other long-term care facilities
- Contacts of high risk patients

Influenza vaccination may also be helpful in people with asthma, aspirin therapy, pregnancy, high-risk workplace, and travellers. [30]

The UK National Institute for Clinical Excellence[31, 32] defines people at risk for complications from influenza as those who:

- Have chronic respiratory disease
- Have significant cardiovascular disease
- Have chronic renal disease
- Are immunocompromised
- Have diabetes mellitus
- Are aged 65 years and over

INSTITUTIONAL OUTBREAKS

Acute hospital outbreaks

Acute hospital influenza outbreaks are reported infrequently, and often involve only small numbers of patients with low mortality rates.[33] Influenza is the most important cause of hospitalisation for acute respiratory illness in children during influenza outbreaks.[34] A majority of adults with influenza present to their general practitioner more than two days from the onset of symptoms precluding the use of antiviral treatment.[35] There is no reason to believe the situation will be any different for patients presenting to hospital with influenza. Even though patients admitted to hospital with influenza may be precluded from treatment with antivirals due to presentation after 48 hours of onset of illness, public health measures such as patient isolation and appropriate supportive and other treatment measures should be administered.[36, 37]

Residential care facility outbreaks

The largest group of patients at risk of institutional outbreaks of influenza are the elderly in any form of long-term care (long-term geriatric/psycho-geriatric hospitalisation, private nursing homes and residential homes).[36] Complications of influenza are common in patients in residential care and they are reported to have a 10-42% risk of developing pneumonia during influenza outbreaks and a case-fatality rate of 30-55% during influenza outbreaks.[38] Outbreaks can also occur in well-immunised populations of patients in residential care[28, 39] if there is not a good match between the vaccine and the circulating strains, if staff vaccination rates are low, and as less than 30% of frail elderly patients seroconvert after vaccination.[40] Influenza outbreaks can also occur in neonatal and paediatric units and in immuno-suppressed adults.[36, 37]

Recognition of institutional outbreaks

Prompt recognition of institutional outbreaks of influenza is critical[36, 37, 41] and the use of rapid POC influenza testing is encouraged in combination with IF, viral culture and/or PCR.[27] Influenza should be suspected when a hospitalised patient/long-term resident develops unexplained fever and/or respiratory illness during influenza season.[37]

Outbreak and case definitions of influenza outbreaks in residential care facilities and investigation and management of outbreaks (including outbreak control measures) in residential care facilities should occur as per Australian guidelines.[42]

Outbreak control

Vaccination

Annual vaccination of people at risk of influenza and healthcare providers is the primary approach to preventing nosocomial influenza.[36, 37, 39, 41] However, influenza outbreaks continue to be reported even in communities with high rates of vaccination as discussed above.

Infection control measures

Infection control measures during outbreaks are important, however, basic infection control methods such as isolating infected patients/residents, restricting circulation of nursing staff, restricting visitors, effective hand-washing and sterilisation of respiratory devices may be easier to achieve in the acute hospital setting than in residential care settings.[36] Nevertheless, infection control measures such as staff hand washing, staff mask wearing, restricting patients to their rooms and other measures are recommended in residential care facilities.[42]

In acute care hospitals, droplet precautions (private room, mask for healthcare workers and mask for patients when they leave the room) should be employed for patients with documented or suspected influenza until the diagnosis is confirmed or disproved. Community members with fever and respiratory illness should be discouraged from visiting hospitals. Sending home workers with symptoms of influenza can also help control spread.[37]

Chemoprophylaxis

Chemoprophylaxis for hospitalised patients, unvaccinated personnel and those vaccinated less than two weeks before exposure in an institutional outbreak is possible, but the optimal duration of chemoprophylaxis for a nosocomial outbreak is uncertain and should be guided by ongoing surveillance at individual hospitals/wards.[37]

In Australia, antiviral agents are recommended for use by all residents and staff of residential care facilities for both treatment of cases and prevention of new cases in an influenza outbreak and Australian guidelines recommend chemoprophylaxis for all asymptomatic residents (regardless of vaccination status) until the outbreak is over and to all unvaccinated staff for at least two weeks.[42]

Data from NSW Health suggests antiviral agents may have played a role in controlling recent influenza outbreaks in five residential care facilities in NSW (personal communication Dr Jeremy McAnulty, Director, Communicable Diseases Branch, NSW Department of Health). As per Australian guidelines,[42] public health units guide the decision to use antivirals in case of an outbreak. Antivirals are likely to work well in controlling an outbreak in a residential care facility when: the agent is effective against the virus; they are used alongside other infection control measures; chemoprophylaxis is administered to ***all*** asymptomatic residents until the outbreak is over and to all unvaccinated staff for at least two weeks.[42]

COST-EFFECTIVENESS

To date, the Pharmaceutical Benefits Advisory Committee has not recommended any antiviral for subsidy under the PBS for treatment or prophylaxis of influenza. There are no published data on formal cost-effectiveness analysis of anti-viral therapy or prophylaxis in the Australian environment.

Treatment

On the basis of an analysis undertaken in the UK in 2003,[43, 44] vaccination appeared to be a cost-effective strategy for high-risk populations, including children and residential elderly populations. Acceptable cost-effectiveness was not clearly demonstrated for anti-viral therapy or prophylaxis for influenza in any patient population. Another economic evaluation that took into account effectiveness, safety and efficacy of antivirals concluded “the most cost-effective option is not to take any action” in treating otherwise healthy adults with influenza.[45] Likewise, from the perspective of a UK Government payer, zanamivir has been judged not to be a cost-effective option in treating patients with influenza who are not at risk of complications,[46] although it may prove cost-effective in at-risk patients.[47] Furthermore, a Canadian analysis showed that from a government payer perspective, oseltamivir was unlikely to be cost-effective for treating suspected influenza in otherwise healthy adults and oseltamivir was unlikely to be a cost-effective treatment for adults at risk of developing influenza-related complications, although clinical evidence is inconclusive.[48]

Prophylaxis

A recent cost-effectiveness evaluation, based on a decision analytic model of influenza post-exposure prophylaxis (PEP) with oseltamivir in a residential care environment in Canada,

showed oseltamivir was less expensive than either no PEP or amantadine PEP, and was associated with fewer influenza-like illness cases. The authors estimated that one influenza-like illness case would be prevented in 100 patients treated with a 12 day course of oseltamivir.[38]

The National Institute for Clinical Excellence in the UK recommends oseltamivir prophylaxis to all at-risk patients who are exposed to someone with an influenza-like illness when influenza is known to be circulating as long as they can start prophylaxis within 48 hours of exposure.[32] However, following this advice in a nursing home environment and providing prophylaxis to all nursing home residents each time a single case of influenza like illness occurs in staff or residents when influenza is known to be circulating would "require substantial resources", approximately 360,000 courses during an English winter.[49] Thus it has been suggested that oseltamivir PEP be reserved for situations where influenza is laboratory confirmed or strongly suspected due to epidemiologic surveillance.[49] As discussed previously, rapid POC testing should be used to guide treatment decisions.

MANAGEMENT OF SUSPECTED H5N1 INFLUENZA

Patients with suspected H5N1 influenza (or other pandemic strain) should be considered for treatment with a neuraminidase inhibitor pending laboratory test results. The virus is susceptible to oseltamivir and zanamivir in vitro, but the optimal dose and duration of NIs in H5N1 influenza is uncertain. Some resistance to oseltamivir has been detected in some patients with H5N1 influenza.[50] Chemoprophylaxis with oseltamivir is warranted for hospitalised patients who have had a possible exposure to avian influenza. Chemoprophylaxis may be warranted in hospitalised patients in some situations such as if inter-person transmission is increasing in efficiency (hospitals would need to be guided by epidemiological surveillance in these situations).[50] Further guidance on the use of antivirals in an avian influenza pandemic is available from the WHO,[51] NSW Health,[7] and the Commonwealth Department of Health and Ageing Avian Influenza webpage[52] and pandemic plan.[2]

ANTIVIRAL RESISTANCE

Data collected by the WHO Collaborating Centre for Reference and Research on Influenza in 2003 showed that at that time there was no clinically significant resistance to NIs in Australia.[53] However, the Approved Product Information for amantadine notes that resistance to amantadine in influenza A occurs readily.[11] There are however, reports of drug-resistant H5N1 influenza strains emerging in Asia[54] and resistance to normal seasonal strains in Japan during a year when there had been substantial NI use.[55]

EFFICACY & EFFECTIVENESS OF ANTIVIRAL AGENTS

A number of systematic reviews and meta-analyses have been produced (see Table 3). Findings from these include:

- NIs reduce illness by 1-1.5 days in adults and children.[5, 43-45, 48, 56-59] However, the time to resolution of symptoms appears reduced in at-risk people.[48, 56]
- Amantadine shortens duration of fever compared with placebo by about one day[5]
- Efficacy of NIs in preventing clinically defined influenza ranged from 74-90%[5, 43-45]
- The efficacy of amantadine in preventing influenza ranged from 60-90%[5, 45, 57]
- NIs are not cost effective in otherwise healthy adults[48]
- Elderly people in residential care are the only group in whom use of NIs is potentially cost effective[43, 44]
- There is insufficient evidence to show that antivirals prevent complications in at risk people as trials have been mostly conducted in otherwise healthy adults.[48]
- NIs should be reserved for serious epidemics or pandemics in conjunction with other public health measures.[5]

There has been some controversy[60-63] regarding the most recent systematic review,[5] in particular questioning the authors' conclusions that NIs not be used in seasonal influenza due to their ineffectiveness against influenza-like illness. The controversy arises because if there is a confirmed local epidemic or pandemic, the chance of patients with influenza-like illness having "real" influenza is higher and the effectiveness of antiviral therapy therefore would be expected to be higher. The authors recommended the use of antivirals be reserved for a

"serious" epidemic, although they did not define this term. However, the results and conclusions of that review are very similar to the results and conclusions of other systematic reviews (Tables 3).

GUIDELINES FOR ANTIVIRAL USE

A number of clinical practice guidelines have been produced. Recommendations from these documents are summarised in Table 4 below. Recommendations from these documents include:

- Amantadine not be used for influenza treatment and prophylaxis due to high levels of resistance[31, 32, 64]
- NIs only be considered for treatment in at risk adults or children[31, 32]
- NIs are not recommended for routine influenza prophylaxis.[32]
- NIs are recommended for post-exposure prophylaxis in selected at risk people eg all residents (regardless of vaccination status) and unvaccinated staff of residential care facilities in the event of an influenza outbreak and as long as prophylaxis can begin within 48 hours of exposure[31, 32, 59, 65]
- Treatment and prophylaxis of influenza outbreaks in residential care facilities need to be carried out in the context of other infection control measures[42]
- Clinicians should be aware of influenza disease activity in the community or have access to rapid, accurate microbiologic diagnosis for influenza[59, 65]

RECOMMENDATIONS

On the basis of currently available evidence, NSW TAG provides the following recommendations:

1. Effective infection control measures, based on strategies to limit transmission (i.e. contact and droplet precautions), should be utilised to reduce the risk of an institutional outbreak of influenza.

2. Vaccination of at risk[i] people and healthcare workers remains the primary means of preventing seasonal influenza, in conjunction with good infection control and hygiene measures as above.

3. Amantadine should not be used for treatment or prophylaxis of influenza due to high rates of resistance.

4. Neuraminidase inhibitors should not be used for treatment or routine prophylaxis of seasonal influenza in people not at risk of complications, due to their lack of cost-effectiveness and minor clinical benefits in this population.

5. Mortality from nosocomial outbreaks among already hospitalised patients is reportedly low. Also, of those patients presenting to the emergency department with influenza, many will present after the first 48 hours of illness thus precluding the effective use of antivirals. Therefore the role for antiviral agents in treatment and post-exposure prophylaxis is limited in the acute hospital setting.

6. In the event of an institutional outbreak of seasonal influenza in the residential care setting, there is a role for antiviral agents in treatment and post-exposure prophylaxis of elderly people or other at risk people. Stock holdings in hospitals to cover these circumstances may be appropriate. Use of rapid point of care testing for influenza to guide treatment decisions at the beginning of the outbreak is recommended. The decision to use antivirals in an outbreak in the residential care setting should be guided by the local public health unit.

7. Both rapid testing and provision of an antiviral agent for a nursing home outbreak of influenza will require a rapid response procedure to be developed to ensure equity of access and consistency of approach across the State. This will require coordination between the

[i] See page 9 for definition of at risk patients

nursing home, general practitioners, public health unit, laboratories and hospital pharmacies if the 48 hour timeline is to be met.

8. Neuraminidase inhibitors should be reserved for serious epidemics or pandemics in conjunction with other public health measures. If H5N1 influenza (or any other new pandemic strain) is suspected refer to NSW Health Department, Commonwealth Department of Health and Ageing and World Health Organization guidance.

Table 3: Systematic reviews and meta-analyses on efficacy and effectiveness of antivirals for treatment and prophylaxis of influenza

Source	Study question	Studies included	Relevant Results (efficacy)
Cochrane Vaccines Field in collaboration with the University of Queensland [5]	Comparison of prophylaxis and treatment efficacy against symptomatic and asymptomatic influenza	51 reports of 52 randomised controlled trials	1. For prophylaxis, amantadine prevented 61% of influenza A cases and 25% of cases of influenza-like illness but neither oseltamivir or zanamivir had any effect in any dose 2. For treatment: a) Amantadine shortened duration of fever compared with placebo by 0·99 days. b) The efficacy of oral oseltamivir 75 mg and 150 mg daily and zanamivir 10 mg daily was 61%, 73% and 62%. c) Compared with placebo the hazard ratios for time to alleviation of symptoms were 1·33 for zanamivir and 1·30 for oseltamivir provided medication was started within 48 hours of symptom onset. 3. For PEP, oseltamivir had a protective efficacy of 58.5% in households and 68-89% in contacts of index cases. **Recommendations:** 1. Use of amantadine should be discouraged 2. NIs should not be used in seasonal influenza control because of their low effectiveness 3. NIs should be reserved for a serious epidemic or pandemic in conjunction with other public health measures
Cochrane Acute Respiratory Infections Group [56]	Efficacy, safety and tolerability of NIs in treatment and prophylaxis of influenza in children	Three double-blind randomised controlled trials reporting data from 1500 children with clinical influenza of whom 798 had laboratory confirmed influenza	1. Oseltamivir and zanamivir reduced the median duration of illness by 36 hours and 34 hours and reduced time to return to normal activity in previously healthy children with laboratory confirmed influenza 2. Only oseltamivir resulted in significant reduction in complications (especially otitis media) 3. Oseltamivir did not reduce time to resolution of illness in “at risk” children. There was no data on zanamivir in “at risk” children
Cochrane Vaccines Field [57]	Efficacy of NIs in preventing influenza and shortening or reducing influenza severity **in** healthy adults	Eight randomised or quasi-randomised placebo controlled studies with 1180 adults	1. In healthy adults NIs were 74% effective in preventing clinically defined influenza and 60% effective in preventing laboratory confirmed influenza 2. NIs shortened duration of treatment by one day 3. Time gained to return to normal activities was half a day
Health Reviews Ltd (Cochrane) [58]	Effectiveness and safety of amantadine and rimantadine in healthy	*20 preventive and safety trials *11 published treatment trials	1. Amantadine prevented 25% of influenza like illness and 61% of influenza A 2. Amantadine reduced fever by one day

	adults		
Demicheli et al in association with Cochrane Vaccines Field [45]	Three reviews efficacy and effectiveness of vaccination amantadine/rimantadine and NIs in treatment and prevention	*20 papers describing 39 trials of vaccine efficacy *17 preventive trials and 10 treatment trials for amantadine/rimantadine *6 preventive trials and 5 treatment trials for NIs	1. Vaccines reduced clinical influenza by 13-24% and reduced time off work by 0.4 days 2. The efficacy of amantadine in preventing influenza was 61%, shortening duration of fever by one day 3. The efficacy of NIs in preventing influenza was 74%, shortening duration of symptoms by one day 4. Concluded in healthy adults (aged 14-60) with influenza the most cost-effective option is to take no action
Canadian Coordinating Office for Health Technology Assessment [48]	Efficacy and effectiveness on individuals with suspected influenza in terms of the following primary outcomes: death, hospitalisation, complications, time to return to normal activity PLUS cost-effectiveness in the primary care setting compared to no treatment	Six phase III randomised controlled trials (from initial 117) involving 1735 adults (12 years and over) of whom 469 were at risk of complications. All trials sponsored by industry.	1. Insufficient evidence that oseltamivir reduces complications, hospitalisations and/or death in people with suspected influenza – absolute risk reduction of 0.0% for death or hospitalisation in treated patients 2. Insufficient evidence of benefit in people at risk of complications (otitis, sinusitis, bronchitis, pneumonia) – absolute risk reduction of 0.0% for complications in at risk and healthy people 3. One trial suggests otherwise healthy people can return to normal activity 57 hours (95% CI 2.4 to 111.6 hours) sooner than those with no treatment 4. Time to resolution of symptoms in healthy people was 30.6 hours sooner in treated than non-treated patients 5. Time to resolution of symptoms in at risk people was 17.0 hours sooner than untreated people 6. Relative risk reduction of hospitalisation in treated patients was 0.73 (95% CI 0.04-11.81) 7. Relative risk reduction for complications requiring antibiotics was 0.44 (95% CI 0.16-1.16) in healthy people and 0.94 (95% CI 0.50-1.74) in at risk people 8. From a government payer perspective, oseltamivir is unlikely to be cost-effective for treating suspected influenza in otherwise healthy adults 9. Oseltamivir is unlikely to be a cost-effective treatment for adults at risk of developing influenza-related complications, although clinical evidence is inconclusive
National Institute of Clinical Excellence [43, 44]	Clinical effectiveness of oseltamivir and zanamivir for treatment and prevention of influenza A	Randomised controlled double blind trials – 17 treatment and seven prevention	1. Oseltamivir 75 mg twice daily for five days reduced the median duration of symptoms in influenza groups by 0.5 days (95% CI -0.96 to1.88) in high risk groups, by 1.38 (95% CI 0.80 to 1.96) days in otherwise healthy adult population and by 1.5 (95% CI 0.8 to 2.2) days in children.

	and B		2. There was a 29-43% risk reduction in the odds of complications requiring antibiotics when antivirals were given within 48 hours of onset of symptoms 3. Oseltamivir 75 mg once daily produced a relative risk reduction of developing influenza of 75-90% 4. The cost-effectiveness of antivirals was unfavourable except for elderly people in residential care
Canadian Task Force on Preventive Health Care [66]	Efficacy of influenza prevention (vaccination and chemoprophylaxis) in the general population	Thirty-three randomised controlled trials assessed vaccination and six assessed chemoprophylaxis	1. Relative risk reduction of influenza in vaccinated adults was 0-91% 2. Relative risk reduction of influenza in vaccinated children was 0-93% 3. Relative risk reduction of influenza in those taking chemoprophylaxis given within 36-48 hours of symptom onset ranged from 32-84% **Recommendations:** Appropriate use of chemoprophylaxis requires access to rapid diagnosis or an active viral surveillance program

Table 4: Summary of current guideline recommendations for antiviral treatment and prophylaxis of seasonal epidemic influenza

Source	Year	Topic	Recommendations for antiviral treatment and prophylaxis
Centers for Disease Control and Prevention [64]	2006	Influenza treatment and prophylaxis	1. Amantadine not be used for treatment of influenza during the current influenza season due to high levels of resistance[67, 68] 2. Oseltamivir or zanamivir for prophylaxis and treatment of influenza is encouraged 3. Priority should be given to high risk patients (not defined) 4. When antiviral supply may not meet demand, treatment of non-high risk people is not recommended
Communicable Disease Network Australia[42]	2005	Prevention and Control of Influenza Outbreaks in Residential Care Facilities	1. Antivirals are recommended for treatment and prophylaxis of influenza for all residents (regardless of vaccination status) and unvaccinated staff in the event of an influenza outbreak 2. In general, oseltamivir is the preferred option for resident. Zanamivir and amantadine can be considered for staff members 3. Public health units guide the decision to start antivirals 4. Treatment and prophylaxis of influenza outbreaks in residential care facilities need to be carried out in the context of other infection control measures 5. Contact between those taking antivirals for treatment and those taking antivirals for prophylaxis should be minimised 6. Residents should take chemoprophylaxis until the outbreak is declared over and staff should take chemoprophylaxis for two weeks
Canadian Task Force on Preventive Health Care [59]	2004	Influenza prophylaxis	1. Prophylaxis against influenza with NIs in the household setting is supported if it can be initiated within 36–48 hours of symptom onset in the index case 2. Clinicians should be aware of influenza disease activity in the community or have access to rapid, accurate microbiologic diagnosis for influenza
National Institute for Clinical Excellence [31]	2003	Influenza treatment when influenza A or B is known to be circulating	1. Zanamivir and oseltamivir not be used for treatment of influenza in children or adults unless they are considered to be at risk[i] 2. Zanamivir or oseltamivir be used in at risk adults (12 years or older) who present with influenza like illness and can start treatment within 48 hours of onset of symptoms 3. Oseltamivir be used in at risk children (12 years or older) who present with influenza like illness and can start treatment within 48 hours of onset of symptoms 4. Amantadine not be used for treatment of influenza
National Institute for Clinical	2003	Influenza prophylaxis when	1. Oseltamivir be used for influenza PEP in at-risk people aged 13 years and over if: a) they are not effectively protected by vaccination[i]; b) they have been exposed to someone with influenza like illness; and c) they can begin prophylaxis within 48 hours of exposure

[i] At risk people include those who: have chronic respiratory disease; have significant cardiovascular disease (excluding hypertension only); have chronic renal disease; are immuno-compromised; have diabetes; are aged 65 and over.

Excellence [32]		influenza A or B is known to be circulating	2. Oseltamivir not be used for PEP in otherwise healthy people under age 65 3. Oseltamivir not be used for seasonal prophylaxis of influenza 4. Amantadine is not recommended for PEP or seasonal prophylaxis
Swedish consensus group [65]	2003	Influenza treatment and prophylaxis	1. Antivirals not be used in otherwise healthy adults as influenza is generally a self-limiting illness 2. Antivirals be used on an individual basis in those suffering from severe influenza provided: a) influenza is known to be circulating; b) clinical profile is typical for influenza; c) other illnesses have been excluded; and d) treatment can start within 48 hours of symptom onset 3. Zanamivir is recommended if influenza B is the circulating strain

[i] People are not effectively protected by vaccination if vaccination is contraindicated or has not yet taken effect or if the vaccination is not well matched to the circulating strain of influenza.

REVIEWERS
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Dr Dominic Dwyer, Senior Medical Virologist and Infectious Diseases Physician at Westmead Hospital, Sydney

Dr Michael Hills, Associate Director Critical Response Coordination, South Eastern Sydney & Illawarra Health Service, Sydney

Dr Sarah Hilmer, Geriatrician and Clinical Pharmacologist, Royal North Shore Hospital, Sydney

Professor Paul Seale, Respiratory Physician and Clinical Pharmacologist, Royal Prince Alfred Hospital and University of Sydney

DUALITIES OF INTEREST
Dominic Dwyer is employed as a full-time staff specialist in virology at the Institute of Clinical Pathology & Medical Research, Westmead Hospital. He has participated in clinical trials of neuraminidase inhibitors and laboratory trials of influenza diagnostic tests. He has participated in advisory boards for pharmaceutical companies that produce antiviral drugs, including the neuraminidase inhibitors.

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