Submission by The British Thoracic Society to National Institute for Health and Clinical Excellence Health Technology appraisal: *Oseltamivir, amantadine and zanamivir for the treatment of influenza (including a review of existing guidance no. 58)*

Executive Summary

Influenza is a respiratory disease caused by influenza A and B viruses. Our main defence against influenza is provided by neutralising antibodies which target the virus coat proteins haemagglutinin and neuraminidase. Influenza A and B are RNA viruses whose replication is error prone. Random errors in its genetic make up lead to changes in the structure of its surface coat proteins, which in turn allow the virus to partially or completely escape neutralising antibodies, and result in influenza outbreaks, epidemics and pandemics.

In the UK our current prevention strategy is based on influenza vaccination of at risk groups. The WHO estimate that influenza vaccines that are well matched to circulating strains reduce influenza morbidity by about 60% and mortality by 70-80%. Turning to respiratory diseases, in individuals with COPD inactivated influenza vaccines reduce the total number of exacerbations but uncertainty remains about the effects of influenza vaccination in individuals with asthma, bronchiectasis and Cystic Fibrosis.

Amantadine and the neuraminidase inhibitors oseltamivir and zanamivir have specific anti-influenza activity. Amantadine inhibits the viral M2 protein but is effective only against influenza A viruses. It has been clinically tested in influenza outbreaks, epidemics, and a pandemic. When systematically reviewed amantadine reduces the course of influenza A by about a day. The main concern with amantadine therapy is the rapid emergence of resistant viruses. This means that amantadine cannot be used simultaneously for treatment and prophylaxis during an outbreak.

Oseltamivir and zanamivir inhibit influenza neuraminidase and are highly effective *in vitro* against both influenza A and B viruses. These drugs have only been tested in clinical trials conducted during very minor influenza outbreaks (influenza activity in the early part of the 21st century has been far below that observed for most of the 20th century). When systematically reviewed both drugs reduce the course of influenza by about a day in otherwise healthy adults. Only a few trials of these drugs have been conducted in at risk groups and their efficacy in these individuals has not been systematically reviewed.

Currently NICE recommends that Influenza immunisation is the most effective way of preventing influenza. NICE has also recommended that amantadine should not be used for the treatment of influenza, and that zanamivir or oseltamivir should not be used to treat a flu-like illness in people who are otherwise healthy. NICE recommends that when influenza virus A or B are circulating in the community, zanamivir or oseltamivir should be used to treat a flu-like illness in people who are considered to be at risk of developing complications, provided that they can start treatment within 48 hours of their symptoms starting.

Key issues regarding this guidance include firstly that during influenza outbreaks not all communities in the UK will be affected at the same time, and thus early in the outbreak though influenza like illness may have reached high local levels the national average may remain below the threshold which triggers the use of the drugs. Secondly outbreaks of influenza occur in closed communities at times when the levels of influenza circulating in the community is low. These outbreaks often have high morbidity and in the case of the elderly high mortality. Thirdly the natural history of influenza infection differs in individuals who are severely immuno-compromised consideration should be given to removing the 48 hour limit to the use of specific anti-influenza drugs for treatment in this at risk group. Finally given the specificity of neuraminidase inhibitors, and the occurrence of outbreaks of influenza in closed communities/wards out of season, there is there is a need for wider availability of urgent molecular virological testing for influenza.

What is the place of the technology in current practice?

Background

Influenza is the medical term for a respiratory disease caused by influenza A, B or C viruses. These are small "negative strand" RNA viruses. Influenza A usually causes more severe infections than influenza B, while influenza C usually only causes mild common cold like symptoms. Influenza B and C primarily affect humans, in contrast influenza A viruses causes significant morbidity and mortality in a wide range of animal species including pigs, horses and domestic poultry. Influenza A viruses are subdivided on the basis of their surface coat proteins haemagglutinin (15 subtypes) and neuraminidase (9 subtypes), and named according to the subtype of heamagglutinin and neuraminidase that they contain (for example H3N2, H1N1 etc). Limited numbers of subtypes of influenza viruses are found in most affected species, with the exception of aquatic birds from which a very wide range of influenza subtypes can be isolated and these birds are probably the ultimate origin of most if not all new influenza A subtypes.

In countries in the northern and southern hemispheres influenza usually occurs in outbreaks during the winter months, the virus is thought to circulate all year round in equatorial regions.

Influenza viruses are usually spread from person to person in small droplets of saliva coughed or sneezed into the atmosphere by an infected person, though direct contact with hands contaminated with the virus can also spread infection. School children play an important role in virus transmission in the community.

During an outbreak of influenza in a non-pandemic or non-epidemic year for most people influenza infection is either asymptomatic or leads to a self limiting coryzal (common cold like) illness. A significant minority will however develop typical influenza like symptoms which include an abrupt onset of headache, shivering, and dry cough about 48 hours after infection. This is followed by a sudden rise in temperature to 38-40 ^{o}C, intensification of the headache, weakness, myalgia, disturbed sleep, nasal obstruction, cough and substernal soreness. Symptoms last between 2 and 5 days. For some individuals influenza infection can lead to more serious illnesses. The most common complications of influenza are bronchitis and primary viral and secondary bacterial pneumonia, both of which can be life threatening to at risk groups. At risk groups are currently defined in the UK as [1]: Those aged 65 years and over, and those aged 6 months and over with underlying medical conditions such as chronic respiratory disease (including asthma), chronic heart disease, chronic renal disease, chronic liver disease, chronic neurological disease (including stroke and transient ischemic attack (TIA)), Diabetes, people with impaired immunity due to disease or treatment, individuals with Multiple Sclerosis and related conditions, and those with hereditary and degenerative diseases of the Central Nervous System. In the United States of America the Centre for Disease Control include healthy adults above the age of 50.[2]

Primary viral pneumonia is probably under-diagnosed in clinical practice: A prospective study of aetiology of adult lower-respiratory-tract infections in the community detected influenza in 5% of patients using serology and culture[3] (and not the more sensitive molecular techniques), while an earlier study of patients admitted to hospital with community acquired pneumonia reported a rate of 7%.[4] As well as being an important cause of pneumonia influenza in their own right influenza virus infection can lead to secondary bacterial infections. Viruses also play an important role in exacerbations in individuals with both asthma and COPD. Respiratory viral infections precipitate 80% or more of asthma exacerbations in children, and the majority of exacerbations of asthma

and COPD in adults, and although about 2/3 of these infections are by rhinoviruses influenza is also an important contributor.[5,6]

Our principal defence against regular infection by influenza is provided by antibodies particularly neutralising antibodies which interfere with the viral surface coat proteins, haemagglutinin and neuraminidase, and as a result decrease (or abolish) viral entry into host cells. Once infection is established both the innate immune system (acute phase proteins, neutrophils and macrophages) and cytotoxic lymphocytes (CD8+ T-cells) and helper T cells (CD4+ T-cells) play important roles in viral clearance.[7] If an individual does not have neutralising antibodies or primed T-cells for example if they have never been exposed to influenza virus or the influenza virus has undergone a large change in its antigenic structure the acquired immune system will not be able to immediately respond to the infection and will take time to produce influenza antibodies and specific T-cells. During this time the innate immune system will be the only defence against the infection and the chances of death or significant morbidity are much higher.[7]

As noted above the genetic material in Influenza viruses is contained in small discrete strands of single stranded RNA.[8] The RNA is "negative stranded" meaning that it cannot directly transcribe proteins. In most other living organisms genetic information is stored in double stranded DNA. The replication of RNA viruses is much more error prone than the replication of DNA viruses (1 in 10^4 bases compared to 1 in 10^9 bases), these replication errors leads to random changes in virus structure some of which result in strains which are either partially or completely escape our neutralizing antibodies. Small numbers of changes in the structure of these proteins, termed antigenic drift, lead to seasonal outbreaks and epidemics while larger changes in the structure, termed antigenic shift, of the virus which result in pandemics. Pandemic influenza is a devastating illness with attack rates of 20% of the population and high death rates. For example it is now thought that at least 40 million people died worldwide in the 1918 "Spanish Flu" pandemic.[9] The morbidity and mortality associated with influenza in between these pandemics varies considerably, In recent years we have observed very low levels of influenza compared to most of the preceding 20th century, indeed the last influenza epidemic was in the United Kingdom 1990.[10]

The number of people who consult their GP with flu-like illness during the winter is usually between 50 and 200 for every 100,000 population.[10] An epidemic can be declared if more than 400 people per 100,000 of the population consult their GP with flu or a flu-like illness each week. During the 2006/2007 season clinical activity started in early February, and peaked at 43.7 cases per 100,000 in mid February. In the winter of 2005/6, the majority of flu activity was confined to type B with only a few cases of flu A reported.[10] The Health Protection Agency have estimated that during the influenza seasons between 1988/9 and 2005/6 influenza caused between 0 (1997/8, 2005/6) and 26,945 (1989/90) additional deaths per year in England and Wales.[11]

Current treatment strategies in NHS

The current NHS influenza treatment strategy is based on prevention of influenza by mass vaccination of at risk groups. Influenza immunization is available free of charge on the NHS for those aged 65 years and over, as well as for those over 6 months old in at-risk groups under 65 years of age (see above for details), those living in long stay residential care or other long stay care facilities, those who are in receipt of a carer's allowance, or

those who are the main carer of an elderly or disabled person. The inactivated influenza vaccine used in the UK are either split virus preparations or subunit vaccines containing highly purified haemagglutinin and neuraminidase from influenza viruses. The vaccines are produced in hens eggs and the production process is complex and time consuming. It is critical that the vaccine is a good match with the circulating strain. The World Health Organization (WHO) recommends flu vaccine strains based on careful mapping of flu viruses as they move around the world. This monitoring is continuous and allows experts to make predictions of which strains are most likely to cause influenza outbreaks in the northern hemisphere in the coming winter. Current vaccines are trivalent, containing two subtypes of influenza A and one type B virus. In recent years these have closely matched viruses that are circulating.

The efficacy of influenza vaccines has been tested in clinical trials dating back more than 50 years. Such studies often measure the rise in haemagglutination inhibition antibodies (in effect neutralising antibodies) induced by the vaccine as a surrogate marker of protection rather than directly observing influenza rates. A second complication is that many trials observe the effect of vaccination on the frequency of influenza like illness. Unfortunately several viruses particularly Respiratory Syncytial Virus (RSV) can produce a very similar picture to the influenza viruses, and while this has a minimal effect on studies carried out during influenza pandemics it can be a particular problem in years with low levels of influenza activity (as has occurred recently).

In general the effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient, their previous exposure to influenza and/or influenza vaccines and the degree of similarity between the viruses in the vaccine and those in circulation. When vaccines and circulating strains are well matched the influenza vaccination the World Health Organisation quote the vaccines to be 70-90% effective in healthy adults in terms of reducing influenza morbidity, and influenza-related morbidity, while in the elderly influenza related morbidity is said to be reduced by 60% and influenza-related mortality by 70-80%.[12]

However the protection conferred by vaccination to at risk groups in the community when systematically reviewed is considerably less than that noted above and furthermore the protection afforded by repeated vaccination is less than that afforded by first vaccination, probably due to the phenomenon of original antigenic sin[13] (in which antibody (and T-cell) responses to parts of haemagglutinin and neuraminidase that are not subject to antigenic shift and drift are boosted while responses to highly variable parts of the surface coat proteins decline). In a large systematic review healthy adults[14] inactivated parenteral vaccines were 30% effective (95% CI 27% to 41%) against influenza-like illness if content matched WHO recommendations and circulating strain, though this decreased to 12% (95% CI 28% to 0%) when these were unknown. However, effectiveness was considerably lower (16%, 95% CI 9% to 23%) when the studies carried out during the 1968 to 1969 pandemic were excluded.

Against laboratory confirmed influenza vaccines were 80% (95% CI 56% to 91%) efficacious when content matched WHO recommendations and circulating strain but decreased to 50% (95% CI 27% to 65%) when it did not. Again efficacy was lower (74%, 95% CI 45% to 87%) when the studies carried out during the 1968 to 1969 pandemic were excluded. Vaccination had no significant effect on days off work, and there was insufficient evidence to draw conclusions on hospital admissions or complication rates

Turning to the elderly,[15] in individuals resident in homes for elderly the effectiveness of vaccines against influenza like illness was 23% when the vaccine and circulating strain were well matched though the vaccines were not significantly different from no vaccination when matching was poor or unknown. In the subgroup of studies with laboratory

confirmation of infection vaccination did not result in a significant reduction in laboratory proven influenza. However when there was a good vaccine match and high viral circulation, vaccines reduced pneumonia, hospital admission and deaths from influenza or pneumonia.
In elderly individuals living in the community,[15] vaccines are not significantly effective against influenza, influenza like illness, or pneumonia, though well matched vaccines reduced hospital admission for influenza and pneumonia and all-cause mortality.
In individuals with COPD[16] inactivated influenza vaccines reduce the total number of exacerbations (weighted mean difference (WMD) -0.37, 95% confidence interval -0.64 to -0.11, P = 0.006). This is due to the reduction in "late" exacerbations occurring after three or four weeks (WMD -0.39, 95% CI -0.61 to -0.18, P = 0.0004).
Considerable uncertainty remains about the effects of influenza vaccination in individuals with asthma,[17] bronchiectasis[18] and Cystic Fibrosis.[19]

There are a number of drugs including amantadine and the neuraminidase inhibitors oseltamivir and zanamivir with specific anti-viral activity *in vitro* whose efficacy at preventing influenza have been tested in clinical trials. Amantadine functions against influenza A viruses (not type B) by blocking the actions of the internal viral protein M2.
In a Cochrane review[20] Amantadine was found to significantly shorten the duration of fever by about a day when compared to placebo (amantadine by 0.99 days; 95% CI 0.71 to 1.26:). Amantadine had no effect on shedding of influenza A viruses. From the limited data available there was no evidence that amantadine recipients had increased adverse effect rates than the placebo recipients. The authors of this review stated in their discussion that *"the role of these drugs in influenza prophylaxis and treatment is beyond question and does not need to be investigated further compared to placebo"* [20]. One key problem when using Amantadine for the treatment of influenza is the rapid emergence of resistant strains. This means that Amantadine cannot be effectively used for treatment and post exposure prophylaxis in a closed community such as a nursing home during an outbreak.

The second class of anti-influenza drugs are the neuraminidase inhibitors oseltamivir and zanamivir. As there name suggests they inhibit influenza neuraminidase and cause the virus to clump in the respiratory tract and impede viral entry into host cells. These drugs are highly effective *in vitro* against both influenza A and B viruses. In healthy individuals the drugs in order to be effective need to be given early in the course of infection usually within 48 hours of symptoms. This is because early in infection the virus replicates because most subjects with a normal immune system will have cleared the virus by this time point. As noted in the background (above) influenza like illness is often not caused by influenza viruses, and in recent years we have seen very low levels of influenza activity. As a result the data obtained from studies on the efficacy of these drugs can be subdivided into two groups: data on the effects of neuraminidase inhibitors on influenza like illness and data on the efficacy of the drugs in individuals with proven influenza.
The effect of the neuraminidase inhibitors in the treatment of influenza has been the subject of a systematic review by the Cochrane Collaboration [21]. For the time to alleviation of symptoms in the intention to treat group with influenza like illness the estimated hazard ratios for zanamivir was 1.24 (95% CI 1.13 to 1.36). This indicates that the treated group are 24% more likely to have their symptoms alleviated than the placebo group by a given time point. A similar result was obtained for oseltamivir (hazard ratio 1.20, 95% CI 1.06 to 1.35). For individuals who were influenza-positive, the hazard ratios were 1.33 (95% CI 1.29 to 1.37) for zanamivir and 1.30 (95% CI 1.13 to 1.50) for oseltamivir, indicating that

the influenza positive treated group are 30%.
Turning to the studies looking at time to return to normal activities in individuals with influenza like illness the pooled estimated hazard ratio for zanamivir was 1.28 (95% CI 1.13 to 1.45), while the single study assessing oseltamivir had a non-significant hazard ratio (1.23, 95% CI 1.02 to 1.48)[21]. In influenza-positive participants the pooled hazard ratio was just below significance 1.17 (95%CI 1.00 to 1.37, P value 0.06) for zanamivir and significant for oseltamivir (1.22, 95% CI 1.07)[21].

The advantages and disadvantages of the technology

Neuraminidase inhibitors are highly effective against influenza viruses *in vitro*. The data presented above indicate that the drugs are effective in vivo against clinical influenza in healthy adults, where they appear on average to shorten illness by about a day. However, as noted in the background information, in recent years, when the trials of the efficacy of neuraminidase inhibitors were conducted, the levels of influenza like activity seen in the community have been exceptionally low in historical terms and the clinical course of influenza during the outbreaks that have occurred has generally been mild. As a result the clinical trials may have underestimated the efficacy of the drugs against what might be described in historical terms as "typical influenza". There have also been no large scale studies investigating at the effectiveness of these drugs in an influenza epidemic or pandemic.
There have also been very few studies and no systematic reviews on the efficacy of the neuraminidase inhibitors in at risk groups such as individuals with chronic respiratory disease or individuals who are immunocompromised. This is disappointing as this is the area where these drugs are theoretically most likely to decrease morbidity and mortality.

The first disadvantages of neuraminidase inhibitors are their cost: a 5 day course of oseltamivir costs about £16.50: Though when placed against the cost to society (rather than the NHS) of an extra illness these drugs would appear to be highly cost-effective.
A second disadvantage of the neuraminidase inhibitors is that in previously healthy individuals the drugs need to be given within the first 48 hours of illness. This presents a logistical challenge to the NHS in that in an outbreak individuals would need to present to their GPs when unwell to collect a prescription. One way round this would be for at risk groups to have either a prescription on stand by at home with clear instructions on when to collect the drugs from their pharmacist, or alternatively for the higher risk groups to have a supply of neuraminidase inhibitors at home again with clear instructions on its use.
The third theoretical disadvantage of neuraminidase inhibitors is that the widespread of use of neuraminidase inhibitors in non-epidemic/pandemic years might lead to the emergence of strains with resistance to these drugs, which might resort with potential pandemic viruses.

Adverse events relating to technology

Oseltamivir's principal adverse event is nausea.
As noted above there is a theoretical risk that resistant viruses will become established following widespread use of neuraminidase inhibitors.

Any additional sources of evidence

There may have been unpublished trials on the efficacy of neuraminidase inhibitors in military personnel.

There is an urgent need for information on the efficacy of neuraminidase inhibitors post exposure prophylaxis in immuno-compromised individuals, and other at risk groups.

Implementation issues

The current National Institute for Health and Clinical Excellence Health Technology appraisal on oseltamivir, amantadine and zanamivir for the treatment of influenza[22] provides useful guidance for the use of these drugs in the general community. However there are a few key issues which have not been adequately addressed in the guidance.

1) *Threshold level of Influenza Like Illness in community before neuraminidase inhibitors can be used for at risk groups*
   The guidance specifies that Neuraminidase inhibitors should not be used for at risk groups until influenza like illness reaches a critical threshold in the community. There are a number of issues regarding this guidance. Firstly while influenza outbreaks usually last for a few weeks in the UK not all communities in the UK will be affected at the same time, and thus early in the outbreak though influenza like illness may have reached high local levels the national average may remain below the threshold which triggers the use of the drugs. Secondly there is good evidence that outbreaks of influenza occur in closed communities at times when the levels of influenza circulating in the community is low. This has been documented by the HPA in residential homes and in boarding schools in the UK. These outbreaks often have high morbidity and in the case of the elderly high mortality. Similarly the author is aware of an outbreak of influenza in a haematology ward specialising in bone marrow transplantation and chemotherapy which lasted for several months and which continued well beyond the time influenza had ceased to circulate in the general community.

2) *48 Hour limit to treatment (1)*
   The 48 hour time limit to treatment presents a major logistical challenge to the NHS (and the drugs actually work more effectively within 36hours, and probably it is better to take them as soon as possible). Individuals deemed to require treatment would have to within 48 hours decide they had influenza, make an appointment to see their GP who is likely to have had many similar patients presenting as an emergency, and then take a prescription to a chemist. Clearly symptoms might develop on a Friday evening. Given these difficulties people who are likely to require treatment probably should either have a supply of the drugs at home or at least have a prescription for the drugs to hand so that they can be rapidly obtained.

3) *48 hour limit to treatment (2)*
   The limit of 48 hours post exposure for post exposure prophylaxis occurs because most healthy individuals have cleared the virus by this time. As the natural history of influenza infection differs in individuals who are severely immuno-compromised, as they may take weeks/months to clear influenza, some consideration should be given to removing the 48 hour limit to the use of post exposure prophylaxis in this at risk group. Little is known about the clearance of influenza in individuals with

chronic respiratory disease and more research is needed in this area.

4) *Need for wider access to rapid molecular diagnostic tests for influenza*
   Given the specificity of neuraminidase inhibitors, and the occurrence of outbreaks of influenza in closed communities/wards out of season, there is there is a need for wider availability of urgent virological testing with PCR/NASBA based technologies to determine if influenza like illness is indeed due to influenza.

5) *Logistical issues*
   The supply of neuraminidase inhibitors is limited and consideration needs to be given to stockpiling these drugs, and to the supply chain of the drugs to at risk individuals during an influenza epidemic.

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[redacted] on behalf of the British Thoracic Society (November 2007)