HPA submission to NICE for the assessment of zanamivir, oseltamivir and amantadine for the treatment of influenza (an update review of existing guidance No. 58).

February 2008

1 Criteria for triggering the use of neuraminidase inhibitors by clinicians for the treatment of influenza in the UK
2 Use of neuraminidase inhibitors in the treatment of severely ill patients with influenza where treatment cannot be started within 48 hours of onset of illness.
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4 Familiarity with, and access to, anti-viral drugs in the treatment of influenza

1 Criteria for triggering the use (both start-up and stoppage) of neuraminidase inhibitors by clinicians for the treatment of influenza in the UK

Guidance was issued by the National Institute of Clinical Excellence (NICE) on the use of antiviral drugs in the treatment and prevention of influenza in February 2003 and September 2003 respectively. In order to ensure that the use of these drugs would be restricted to patients with influenza-like illness in whom the likelihood of true influenza virus infection was high, the prescription of these drugs was linked in the NICE guidance to the occurrence of influenza virus activity in the community to be determined through information from community-based virological surveillance schemes. Appendix E to the guidance provides details of the thresholds for national sentinel influenza surveillance schemes (in England, Wales, Scotland and Northern Ireland) as well as information about virological monitoring. The appendix states that "monitoring bodies will usually declare that influenza is circulating whenever the baseline (threshold) level is exceeded".

In England, the Department of Health, in discussion with the Health Protection Agency (HPA) and the Royal College of General Practitioners, has issued guidance each year to doctors to trigger when they could begin to prescribe antivirals to patients with a relevant illness. The interpretation of this guidance in England has been to withhold this trigger until the threshold level of 30 consultations per 100,000 population (reduced from the previous threshold level of 50 in 1997) has been reached in the RCGP sentinel practitioner scheme. While in some years this has been an appropriate trigger point, in others it has not and has led to a reduced opportunity for patients, at risk of the complications of influenza, to be offered a potentially effective intervention. There has been a secular decline over the last 25 years in rates of consultations with general practitioners for acute respiratory illnesses which has continued since the threshold was lowered in 1997.

The purpose of this paper is to demonstrate the shortcomings of the current interpretation of guidance on the appropriate trigger point for the use of antivirals against influenza and to recommend a more appropriate approach. A similar approach is recommended for the devolved administrations.

The guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza also ties the use of these drugs to the period when influenza is known, on the basis of community virological surveillance of influenza, to be circulating in the population. Outbreaks in institutions, particularly among the elderly, and due to true influenza virus infection, often occur outside this period. The current guidance denies this vulnerable group, and their carers who may act to spread the infection, access to a potentially effective intervention. This paper also reviews this issue and recommends a more effective approach.

Thresholds and influenza virus activity in England

Influenza activity in England over the six recent seasons, 2001/02 to 2006/07, is summarised below and in the attached figures. Each of the figures shows the rate of consultations with GPs in the RCGP sentinel scheme along with the numbers of isolations of influenza virus in the HPA/RCGP community based virological scheme. In addition, the rate of calls to NHS Direct for 'fever', which increases with the occurrence of influenza infections in the community, and the numbers of outbreaks of influenza infection reported to the HPA, are shown where relevant.

2001/02
Community based virological evidence of circulating viruses coincided with the rise in RCGP consultation rate. The first isolates were reported in week 52, one week before the threshold of 30/100,000 was reached. The threshold remained above the baseline for seven weeks although influenza virus isolates continued to be reported for a further two weeks. The use of the threshold as the trigger for beginning the use of antivirals was appropriate for this season, but would not have been an appropriate trigger to stop the use of the antivirals.

2002/03
The threshold of 30/100,000 was reached only once (week 02) during the season which coincided approximately with the start of sustained reporting of influenza isolates from virological surveillance. Community based virological activity was recorded for 16 subsequent weeks while the RCGP rate remained below the threshold level. Twelve outbreaks were reported during this period, two of which were confirmed as influenza A, five as influenza B and one as both influenza A and B. As in 2001/02, the use of the threshold as the trigger for beginning the use of antivirals would have been appropriate for this season, but would not have been an appropriate trigger to stop the use of the antivirals.

2003/04
Virological evidence of influenza activity was reported for two weeks (weeks 42 and 43) before the threshold of 30/100,000 was reached in week 44. Activity continued subsequently for ten weeks during which time the rate remained above the threshold. Twenty five outbreaks of influenza-like illness were reported during this period, ten of which were confirmed as due to influenza A. Thus the use of the threshold would have triggered the use of antivirals one or two weeks later than the start of documented activity in the community.

2004/05
Although reports of influenza virus isolates were received for eight weeks before the threshold of 30/100,000 was reached in week 52, the numbers of isolates remained low and sporadic until week 51. Reports of isolates from virological surveillance continued for seven weeks after the threshold had fallen below 30. Forty outbreaks were reported, 17 of which were confirmed as influenza A and one as influenza B. In this season, the use of the threshold would have meant that the trigger was perhaps one week late but would not have been an appropriate trigger to stop the use of the antivirals.

2005/06
This was an influenza B year when a large number of outbreaks in schools were reported. The first outbreak was reported in week 45 and the first isolates from community virological surveillance in week 49. Sustained reporting of both isolates from the community and outbreaks occurred from week 52 onwards. Fever reports to NHS Direct went above the 9% threshold (representing a significant increase in this indicator) in week 2. The threshold for consultations in the RCGP scheme of 30/100,000 was only reached in week 5 of 2006 and remained above the baseline for only three weeks. Nine further weeks of influenza activity occurred in the community, based on reports of virus isolation and outbreak reports. Altogether 715 outbreaks of ILI were reported, 73 of which were confirmed as due to influenza B, nine to influenza A and two to both influenza A and B. Thus in this season, the use of the threshold led to very late triggering of the use of antivirals. Subsequently, influenza activity continued for many weeks after the consultation rate has fallen below the threshold.

2006/07
Influenza virus isolates were reported from the community from week 45, and sustained reports from week 51 onwards. The threshold of 30/100,000 consultations in the RCGP scheme was only reached in week 05. It remained above this level for four weeks after which sustained reports of virus isolates continued to be received for a further five weeks. Thirty six outbreaks were reported in this season, 12 due to influenza A infection. Use of the threshold in this season triggered the use of antivirals approximately six weeks late, and influenza activity continued for some weeks after the consultation rate has fallen below the threshold.

Conclusion

The use of a threshold based on consultation rates with general practitioners in England in the RCGP sentinel scheme is inadequate as the basis for the trigger for prescribing influenza antivirals as recommended in the NICE guidance. Consultation rates have been falling steadily over the last ten years and base line levels are barely exceeded in some years, even though there is good evidence from other indices that influenza viruses are circulating. In recent years the linked virological and clinical data show that many weeks of virus activity can occur before the threshold level is reached and after it has fallen back below the threshold level.

The HPA recommends that the trigger for the NHS to activate both start-up and stoppage of prescribing of antivirals for influenza should be announced each season by the Department of Health in England on the basis of the advice of the Health Protection Agency which, in turn, will base its advice on all the relevant epidemiological, clinical and virological surveillance data available. The trigger should not be tied to one particular index of influenza activity.

Use of neuraminidase inhibitors in the treatment of severely ill patients with influenza where treatment cannot be started within 48 hours of onset of illness.

Oseltamivir is licensed for the treatment of influenza within 48 hours of the onset of symptoms. Current NICE guidance recommends that clinicians not offer antivirals after this 48 hour point and bases this advice on the lack of good evidence for effectiveness beyond 48 hours. Recent data, however, suggest that patients with severe influenza requiring hospitalization had a lower risk of death even when oseltamivir was begun more than 48 hours after illness onset (McGeer, CID, 2007). In view of these findings, the relative infrequency of such severe illness (as opposed to mild illness in patients in the community), the relatively low cost of this potentially life saving intervention and the importance of giving a patient with a life threatening illness the benefit of the doubt, there is a strong case for offering such patients anti-viral treatment as soon as possible even if the onset of symptoms was more than 48 hours previously.

Treatment of patients with influenza-like illness outside the period formally designated to be when influenza virus is circulating in the community

Outbreaks of influenza in closed institutions and communities commonly occur ‘out of season’ when community influenza activity (as judged by community based clinical and virological surveillance) has either not yet started or is over (e.g. Read CA, Mohsun A, Nguyen-Van-Tam JS, McKendrick M, Kudesia G. Outbreaks of influenza A in nursing homes in Sheffield during the 1997/98 season: implications for diagnosis and control. J Public Health Med, 2000; 22:116-120).

Outbreaks in this setting may be associated with high levels of exposure for residents and high attack rates. There is evidence, in addition, that the protection conferred on elderly people by influenza vaccination in the autumn may decline within less than 6 months.

The HPA takes the view that, if an outbreak of ILI occurs 'out of season' in a nursing home, and there is virological evidence that influenza is the causative agent, it would be indefensible not to recommend the use of neuraminidase inhibitors both to treat those at high risk of the complications of influenza but also to assist in controlling the outbreak. This view, however, would contradict current NICE guidance which only permits the prescription of anti-virals in the period formally designated to be when influenza virus is circulating in the community.

4 Familiarity with, and access to, anti-viral drugs in the treatment of influenza

One consequence of the restrictions on the use of anti-viral drugs recommended by NICE has, in the view of the HPA, been a reluctance on the part of clinicians to use anti-viral drugs at all. Anecdotal accounts from clinicians suggest that uncertainty, when faced with a patient, that the patient belongs to an appropriate risk group, that the illness began within the recommended period of time and that the country was, or was not, within the period that influenza viruses had been declared to be circulating within the country, means that clinicians rarely prescribe. As a result, prescription levels for these effective medicines are at extremely low levels in the UK.

A major element of the planned response in the UK to a pandemic of influenza is the use of neuraminidase inhibitors in large numbers of patients with influenza-like illness. Clinicians will be unfamiliar with the use of these drugs and will be ill equipped to monitor the prescription of courses to very large numbers of patients during a pandemic.

A much simpler and clearer set of guidelines which, in practice, led to increased appropriate use of these agents, would be highly desirable.