Clinical Expert Statement
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Statement of personal experience:
Consultant Clinical Virologist, head of the respiratory virus unit at the HPA Centre for Infection, and Director of the UK WHO national influenza centre since 1995. My specific interest is in respiratory viral infections and antivirals. This began as a result of my PhD uncovering the mechanism of action of amantadine on influenza replication, and is continued through a substantial applied R&D programme. A particular focus of clinical research is the development of methodology for early detection of antiviral resistance.
As a clinical director of the UK influenza reference laboratory, I am frequently asked for specialist advice (nationally and internationally) on the following subjects

1. Outbreak investigation, treatment and management of respiratory infections (community and hospital)
2. Outbreak investigation, treatment and management of avian influenza infections (hospital and community)
3. Management of unusual/severe clinical cases of influenza (hospital)
4. Management of influenza infections in immunocompromised individuals, with persistent shedding
5. Investigation of drug resistance in treated subjects

I am currently Co-Chair of the Neuraminidase Inhibitor Susceptibility Network (NISN), an international group of academic scientists and clinicians with expertise in influenza and/or antivirals. NISN was set up in 1999 at the request of FDA and other regulatory agencies to ensure that industry met the Phase 4 monitoring requirements for detection of antiviral resistance following licensure of Neuraminidase Inhibitor (NI) drugs. The NISN group collaborates closely with the WHO.

What is the place of the technology in current practice?

How is the condition currently treated in the NHS?

- Vaccination
- Advice
- Antivirals

The mainstay of seasonal influenza management within the NHS is vaccination. The recommended use of antiviral drugs for influenza reflects national vaccine policy and recommendations. Vaccination campaigns are vigorously promoted between Oct and Dec every year, in recognition that influenza A and B circulate during the winter months. Other key messages from Dept of Health at the same time of year, targeted towards healthy adults, for whom vaccine is not recommended, include “flu is a self limiting illness, stay at home, rest, ensure good fluid intake”

Vaccination is targeted towards those most at risk of complications, with the focus of national vaccine campaigns being the elderly over 65. Overall vaccine uptake runs at ~ 75% in this group and ranged from 64.9% to 79.9% in different primary care trusts (PCTs) in winter 2007/08. Vaccination under 65 is directed towards those at risk. Within individual risk groups, overall uptake is approximately 45%, but with substantial local variation from 24.7% to 59.3% in different PCTs.http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1213083216553,

In most years there is a fair to good match between vaccine for circulating H1, H3 and B strains, but approximately every 2-3 years, one of the vaccine antigens will not represent a good match for circulating strains, as occurred in winter 2007-08. It is therefore predictable that neither vaccine coverage nor vaccine match will be 90% complete/accurate in any one year for at risk groups.

The use of antiviral NI drugs within the NHS is currently governed by NICE guidance, meaning that drugs may be given within 48 hours of illness onset, when it is recognised that influenza is circulating, to specific groups in the population.

NI drugs are considered for treatment in hospitals when there is specific laboratory confirmation of influenza diagnosis in an individual patient admitted to hospital. The application of viral diagnosis at the point of admission to hospital (using point of care (POC) tests) is not common in UK hospitals. Requests for diagnostic work-up on individuals admitted with acute respiratory infections usually concentrates on the detection of bacterial pathogens, partly based on the cost of providing viral diagnostics and partly because of physician awareness about availability, reliability and speed of virology diagnosis. Application of virology laboratory diagnostics to respiratory admissions to hospital from the community is therefore not standard practice, but is more likely to occur in immunocompromised individuals, or those admitted severely unwell with a history consistent with viral illness or contact with respiratory outbreak. The combination of lack of routinely applied specific viral diagnosis, and perception of lack of efficacy after 48 hour window (direction to treat within 48 hours) means that there is very little use of NI drugs in hospital settings for respiratory admissions, even for severely unwell individuals, within 48 hours onset.

The requirement for detection of circulating influenza, and “permission from Dept Health” is a pre-requisite for prescribing in the community. An analysis of consulting patterns of individuals with influenza like illness (ILI) in the community indicates that less than a quarter consult within 48 hours post illness onset (Ross et al, 2000), it is unsurprising that GPs do not make much use of the NI drugs for management of uncomplicated influenza, let alone severe influenza or its complications in the community. Routine surveillance of GP prescribing of antivirals for flu like illness in winter 2007/08 indicates hardly any use of. For example, an interrogation of QSURVEILLANCE GP prescribing database http://www.hpa.org.uk/hpr/infections/primarycare.htm (covering a denominator of over 20 million population) during weeks 1-5 of 2008 which includes the peak weeks of influenza in winter 2007-08, revealed that 2 prescriptions for antivirals were provided for 4,831 consulting with ILI from a population denominator

of 21 million (Table 1)This is consistent with independently collated, (IMS data) on total NI prescriptions, (Figure 1) which indicates that the overall prescription of NI drugs in all sectors in the UK is too low to record, in contrast to countries such as Japan, US, Germany and France. ***NI drugs are therefore not part of standard treatment of seasonal influenza, either in hospital or in the community in the UK, irrespective of age group, severity of illness or underlying vaccination status, and may be substantially underused in relation to the burden of severe illness caused by influenza***

Table 1

Week No 2008	ILI Index per 100,000	No of Cases Seen	No of cases for which antivirals prescribed	Population Denominator
1	22	4,841	2	21.8 million
2	32	*	7	*
3	19.8	*	11	*
4	15.1	*	13	*
5	12.3	*	4	*

* data not yet available

Oseltamivir is recommended for treatment of sporadic cases of suspected avian influenza, arising in either poultry workers exposed to H5/H7 in the UK, or returning travellers with relevant exposure to avian influenza

Amantadine is rarely, if ever used in the UK to treat influenza for the following reasons. Amantadine acts as a viral M2 protein inhibitor . It is not active against influenza B. Resistance emerges very rapidly during treatment, approximately one third of treated individuals will shed resistant virus within 72 hours and resistant viruses are easily transmissible. A high proportion of circulating strains are naturally resistant. Nausea and CNS side effects (dizziness & confusion) occur in 5- 10%. Toxic levels of drug may occur if reduced creatinine clearance particularly affecting frail elderly. Amantadine may be considered in persistently infected individuals, known to carry an amantadine sensitive virus.

Is there significant geographical variation in current practice?

There are significant gaps in vaccine coverage across the UK population, particularly marked in working age population who are not recommended for antiviral treatment (see above). Vaccination of children is not recommended unless children fall into a risk group.

Similar variations in the extent of prescribing for NI drugs may be anticipated. The availability and willingness to prescribe NI drugs within hospitals is likely to vary according to local expertise and interest in influenza management. Larger centres with specialist virology/infectious diseases are more likely to have more knowledge of drug efficacy and experience of use, but even in these circumstances there are difficulties for physicians in the availability of drugs from hospital pharmacies who may restrict prescribing strictly on NICE guidelines.

There are national differences in the policy with respect to stockpiling of amantadine. The Welsh Assembly indicated a willingness to stockpile amantadine for treatment and prophylaxis, in contrast to England which has not stockpiled this drug.

Are there differences in opinion between professionals as to what current practice should be?

There is very little prescribing of NI drugs in the community; consequently, there is relatively little experience of NI drugs in routine practice in the community (for reasons described above), and uncertainty about benefits (rather than differences of opinion). A key message about drug efficacy seems to be “day to a day and a half alleviation of symptoms in healthy adults”. Many GPs may be sceptical about the value of the drug for treatment of influenza in the community with this message, particularly when there are key Dept Health messages about “stay at home, self limiting illness etc”, and a desire not to overwhelm GP surgeries with requests for prescriptions. There is often considerable difficulty for physicians in the community managing outbreaks in elderly care facilities, in sourcing drugs, through local pharmacies or hospital pharmacies, as the drugs are not widely used. This is exacerbated when outbreaks occur at the beginning or the end of the influenza season when drug prescribing has not been switched on

Hospital physicians certainly do experience difficulties in regard to availability of drugs when they may be appropriate for treatment of

- unvaccinated healthy adults and children admitted with severe illness,
- adults with severe illness more than 48 hours into course of illness or
- returning travellers with suspect avian influenza
- exposed poultry workers with influenza like illness
- Management of outbreaks in elderly care facilities
- Immunocompromised individuals

and other sporadic situations as many hospital pharmacies may not permit prescribing outside strict NICE guidelines. HPA is aware of several instances every year since the introduction of the NICE guidelines, where this has been the case. This situation is particularly exacerbated in years when there is a mismatch between vaccine and circulating strains.

There are no substantial differences in opinion about the use of amantadine, which is currently extremely limited on account of natural resistance

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

No other specific anti influenza drugs available

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

1. Hospitals

There is little data on the drug treatment of otherwise healthy adult admitted to hospital with severe illness. Recent observational clinical data from Canada (Mc Geer et al, JID 2007) which specifically looked at over 300 respiratory admissions to ITU in winter 06/07 demonstrated that 10% of respiratory admissions to ITU were due to influenza infection when laboratory diagnostics were applied, as the influenza diagnosis was mostly not predicted on clinical judgement or predisposing risk factors. 48% (10/21) of those who did not receive NI antivirals died, compared with 1/13 who did (p= 0.02). All of the antiviral treatment commenced after 48 hours. This type of data emphasises the necessity for better application of virology diagnostics, and the use of antiviral drugs in severe illness outside a rigid 48 hour window. Indeed, it suggests that empiric antiviral therapy for febrile respiratory illness admission to ITU and admission to hospital during winter should be considered. Evidence about the usefulness of NI drug treatment in severe influenza also comes from treatment case series of individuals infected with H5N1

2.*Immunocompromised*

Such individuals with influenza infection have a worse prognosis compared to immunocompetent patients. Respiratory related complications e.g pneumonia,death are increased and there is a prolonged period of viral shedding and higher viral load. {Nichol WG et al, Clin Infect Dis 2004;39:1300 – 1306, Chemaly CID 2007} Such patients definitely benefit from the use of antivirals outside the current NICE 2003 recommendations (beyond 48 hours from symptom onset, or outside the assigned period when influenza is circulating).

3.Children

The burden of illness due to influenza in children is not well recognised, and severe influenza illness may be completely missed in very young children, particularly in years of new antigenic drift variants. This is exemplified in winter 2003/04 when there were unexpected paediatric deaths due to influenza A/Fujian/411/2003 a new H3N2 drift variant (Bhat et al, NEJM 2006). In Britain,during the same winter period there were 17 paediatric deaths directly attributable to influenza in unvaccinated children with no predisposing risk factors. The majority of children were admitted to hospital prior to death. None of these children were treated with antiviral drugs, despite there being an antemortem diagnosis of influenza in several children (HPA & SCIEH unpublished data). Routine use of rapid diagnosis and NI drugs for treatment of influenza in young children may also assist in reducing hospital admissions and unnecessary antibiotic prescribing. (Democratis et al, Poster 1310 Options for Influenza, Toronto 2007).

4.*Individuals infected with non human influenza strains*

The clinical course of individuals infected with non human influenza strains (avian or swine) cannot be predicted from knowledge of human seasonal influenza. It is essential that antiviral drugs are used empirically to treat illness in such individuals and assumptions about lack of efficacy after 48 hours of illness onset are not applied. The best summary of clinical data from worldwide experience of treatment of H5N1 is provided by Gambotto et al, Lancet 2008. The survival rates for those treated within 5 days was 56%, compared with 26% for those treated after 6 days. Clinical illness and viral shedding parameters vary considerably during “zoonotic” inflections with influenza A, and immediate use of NI drugs is essential as soon as the diagnosis is suspected, prior to laboratory confirmation

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? See above.

Use of amantadine not recommended in the elderly with impaired creatinine clearance

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

NI Drugs should be easily available in both primary and secondary care, without arguments about whether the intended use conforms to NICE guidelines, and improvements in providing a flexible“ on switch” implemented. HPA have already provided recommendations in the NICE prophylaxis appraisal (No 67) about improvements that could be made to triggering use of antivirals

Particular consideration should be given to easy fast access to NI drugs for outbreak treatment and management, in elderly long term care homes where outbreaks can be explosive, with high mortatlity. HPA is aware of instances every winter where there have been inappropriate delays of hours or days awaiting the logistics of specimen collection and transport for laboratory diagnosis, prior to the use of NI drugs for treatment in such outbreaks. Improving the use of POC diagnostic devices(dipsticks) by community physicians involved in managing outbreaks and promotion of a “treat and test” approach in these situations, rather than the current practise of “test then treat” should lead to an improved use of the technology.

In my personal opinion, consideration could be given to making NI drugs available as OTC preparations, so as to reduce the health care costs associated with prescribing and improve the use in the community. This may require better mechanisms for disseminating information about circulating influenza (on switch), and better distribution mechanisms involving pharmacists

Improved availability and use of POC devices in hospital admission units in the winter months may assist with the management of serious respiratory admissions, but even if this is not possible, more consideration of empirical use of technology during the periods of influenza circulation should provide a more consistent approach to the management of severe influenza

Early diagnosis and availability of antiviral therapy enables clinicians to safely discharge febrile children presenting to secondary care with influenza (Democratis et al, 2007). This has the potential to reduce hospital admissions among influenza-infected children, including the potential for nosocomial transmission and unnecessary invasive investigations. Formal randomised cost evaluation programmes of rapid antigen testing in paediatric A&E are needed

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Used off license indications for immunocompromised currently

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

1. The current British Thoracic Society (BTS) Guidelines for treatment of community acquired pneumonia do not specifically mention antiviral use.

2. The 2005 European Respiratory Society Guidelines for the Management of Lower Respiratory Tract Infection "Only in high-risk patients who have typical influenza symptoms, for <2 days, and during a known influenza epidemic, can anti-viral treatment be considered. (C1)" {Woodhead M et al, ERJ 2005;26:1138 – 1180}

3. 2007 Infectious Diseases Society of American(IDSA)/ American Thoracic Society (ATS) Guidelines on Community-Acquired Pneumonia states: "Use of oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for >48 h but these drugs may be used to reduce viral shedding in hospitalised patients or for influenza pneumonia {Mandell LA et al. Clin Infect Dis 2007:44:S27 – 72}

4. WHO treatment guidelines for management of H5N1 infections recommend use of oseltamivir irrespective of date of onset of illness http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

Almost all the data on antivirals (NI drugs) relate to use in patients with uncomplicated influenza in healthy adults treated in the community. Recruitment into clinical trials required that patients consulted within 48hours. Less than a quarter of individuals in the UK with ILI consult their GP within 48 hours (Ross et al, 2000), although children are more likely to consult early. It would be helpful to develop observational (rather than RCT) clinical efficacy data based following treatment in the community in the UK .

As discussed, Phase 3 Clinical trials pre-licensure were essentially carried out in the healthy adult in the community. Presumably due to complexity and cost of recruiting sufficient severely ill individuals, these were not included in the overall recruitment profiles of the Phase 3 trials for either zanamivir or oseltamivir. Meta analysis pooling data from more severely unwell individuals demonstrated incremental improvements in the most seriously unwell in the community, although the criteria for specifiying seriously ill did not include hospitalisation (Fleming et al, Options for the control of Influenza Congress series 1219 637-643)

What, in your view, are the most important outcomes and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

- Death
- Hospitalisation
- Prevention of complications
- Reduced prescriptions
- Reduced health care utilisation

These outcomes were not used during the clinical trials, possibly for reasons stated above, as well as because of the ethics of conducting Phase 3 trials on seriously ill patients, before demonstrating efficacy in healthy adults. I am not aware of any RCT trials of efficacy in children.

Long term outcomes have not been assessed in any of the pre or post licensure RCT trials that I am aware of, but there may be HMO database analyses underway

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

1. Neuropsychiatric illness resulting in suicide has been considered as a possible side effect of oseltamivir treatment in Japan, although it is not clear whether this is a side effect of illness, rather than drug treatment, since Japanese individuals have a much higher incidence of encephalopathic complications of influenza
2. Bronchospasm has been noted as a rare and unpredictable complication of zanamivir,
3. Neurological side effects have been noted following amantadine, particularly marked in elderly

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK. Is the technology easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its use?

There are no current alternatives to NI drugs for treatment of influenza. Amantadine may be used in very limited, highly selective situations where there is detailed knowledge of the drug susceptibility of the strain. It is clear that there are
1 Gaps in national vaccination policy, due to failed vaccine uptake or strain mismatch
2.Difficulties in access to NI drugs, both community and hospital
3 Lack of familiarity of prescribing NI drugs in the community
4 Mixed messages about the clinical management of influenza during influenza season*
5 An inflexible "on switch" for prescribing
6 Lack of recognition of potential for treatment of severe illness

* there is a logical inconsistency in national policy in spending millions on vaccination to prevent severe influenza, but then not treating it with antiviral drugs when it occurs because the treatment guidelines are so rigid

Suggest the following

1. More appropriate on and off switch for prescribing (see HPA submission for Appraisal 67)
2. More disseminated use of POC tests in hospital A&E and community outbreaks
3. Improved empiric treatment of hospitalised respiratory illness in adults during winter months
4. OTC availability of NI drugs in the community
5. Early diagnosis and availability of paediatric formulations of antiviral therapy for febrile children with influenza presenting to secondary care.
6. Better liaison and education of pharmacists who may act as an important bridge for the use of technology.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

HPA have already provided recommendations in the NICE prophylaxis appraisal (No 67) about improvements that could be made to triggering use of antivirals

Any additional sources of evidence?

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

There has been some attempt to develop database approaches to evaluation of efficacy of treatment with oseltamivir in prevention of serious adverse events (death and pneumonia) in the United States, using HMO databases e.g P1307 Options for Influenza, Toronto, 2007. I have not seen (but may have missed) peer reviewed publications arising from these original oral presentations

Implementation issues

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NICE guidance is influential, but has led to confusion in regard to appropriateness of treatment. In my view, it has been unnecessarily inhibitory in the use of antiviral drugs for the management of influenza. This is relevant because NICE guidance is primarily focussed on use of drug in the community, and the consequences of rigid guidance aimed at reducing unnecessary consultations in primary care have spilled into hospital practice where the criteria for use should be much more flexible, to meet the challenges of managing severe influenza cases which occur every winter

Pandemic Planning responses require that medical personnel are familiar with technology and interventions that might be used to contain and mitigate a pandemic. At present there is very little experience of use of antiviral drugs in the community, which is a significant impediment to an efficient response to pandemic influenza