Public Health England

Protecting and improving the nation's health

The use of antivirals for the treatment and prophylaxis of influenza

PHE summary of current guidance for healthcare professionals

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through advocacy, partnerships, world-class science, knowledge and intelligence, and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

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Foreword

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Public Health England

This guidance summarises the evidence behind Public Health England's (PHE) recommendations for the use of antivirals for the treatment and prophylaxis of influenza. It should be read with 'The treatment and prophylaxis of influenza: PHE guidance 2014-15'.

The Cochrane Collaboration's review, 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children' (April 2014), as well as the breadth of other available evidence, is discussed.

The recommendations draw on guidance already issued by PHE, the National Institute for Health and Care Excellence (NICE), the Department of Health (DH), the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the European Centre for Disease Prevention and Control (ECDC).

Key messages

- **There is good evidence that antivirals can reduce the risk of death in patients hospitalised with influenza.**
- **In the light of this evidence it is important that doctors treating severely unwell patients continue to prescribe these drugs where appropriate.**
- **PHE continues to support the early use of antivirals for patients with proven or suspected seasonal influenza who are in high-risk groups or who are considerably unwell, (even if not in a high-risk group).**

Background

The range of illness associated with seasonal influenza is wide and the threat of unusual influenza viruses emerging from an animal reservoir is always present.[i]

The only class of drugs that are licensed for the treatment of influenza are the neuraminidase inhibitor (NAI) drugs such as oseltamivir ('Tamiflu') and zanamivir ('Relenza'). The adamantanes ('Lysovir', 'Symmetrel') are no longer useful due to viral resistance.

The licensure of these drugs was dependent on randomised control trials (RCTs) carried out over a number of years on mainly healthy adults with respiratory illness in the community. This represents the milder end of the spectrum of illness due to influenza, which is experienced by up to 15% of the population every year.

Severe illness due to seasonal influenza accounted for 946 ITU/HDU admissions, 1,336 hospitalised confirmed influenza cases and 9,000 excess all-cause deaths in England during the 2012–13 winter season[ii] and represents a different spectrum of illness than has been considered in community RCTs.

Evidence for using antivirals

The majority of RCT evidence for the use of antivirals against influenza is based on otherwise healthy patients in the outpatient setting, who are likely to experience the milder end of the spectrum of influenza illness. However, there is significant observational data examining antiviral efficacy in severe illness.

A recently published article, 'Effectiveness of neuraminidase inhibitors [NAIs] in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data',[iii] in *The Lancet, Respiratory Medicine* adds to a growing body of evidence that treatment with NAIs can reduce the risk of death in patients hospitalized with influenza.

In this meta-analysis, researchers compiled data from 78 observational studies across 38 countries on more than 29,000 patients who were hospitalized with 2009 H1N1 influenza virus infection during the 2009–10 pandemic.

Findings included:

- among patients aged >16 years, treatment with a NAI was associated with a 25% reduction in the likelihood of death compared with no antiviral treatment
- early treatment with NAIs (ie within 48 hours of development of illness) halved the risk of death compared with no antiviral treatment

This supports findings from previous observational studies in hospitalized influenza patients that the clinical benefit of NAI treatment is greatest when started within two days of onset of illness.[iv,v, vi,]

The WHO continues to recommend antiviral treatment with a neuraminidase inhibitor,[vii] ie oseltamivir or zanamivir, as soon as possible for patients with suspected or confirmed H5N1 or H7N9 virus infection; antiviral treatment should not be delayed while laboratory test results are pending. The same recommendation applies to infection with A(H1N1)pdm09 virus where the virus is still causing severe health impacts. Oseltamivir remains on the WHO Essential Medicines list. The CDC[viii] in the USA, and other European public health centres[ix] also continue to recommend the use of antivirals.

Cochrane Collaboration Review

The British Medical Journal (BMJ) and the Cochrane Collaboration have rightly campaigned to gain access to clinical trial data associated with the licensing of new medicines. Their campaign has included accessing trial data for NAIs used in the treatment and prophylaxis of influenza.

As a result of obtaining access to previously unpublished data, the Cochrane Collaboration published an updated systematic review of the efficiency of NAIs for influenza in April 2014.[x]

Like previous reviews on this topic, the 2014 review included evidence from randomised controlled trials (RCTs) in otherwise healthy children and adults, and some who had chronic illness (asthma, diabetes, hypertension), but excluded immunocompromised people. It also included data from RCTs among outpatients, which was previously unpublished.

The BMJ subsequently ran a series of opinion pieces and articles on antivirals.[xi]

Implications of the 2014 Cochrane Review:

The Cochrane review has been reported as suggesting that antivirals are not effective for influenza. This is not the case because of the following aspects of the review:

- variation in outcomes, patient groups, and settings studied limits the conclusions of the review
- the review includes evidence only from RCTs, which by their nature are usually carried out in an otherwise healthy population in the community setting. The review is therefore useful in interpreting the modest effects that NAIs have on the duration of acute symptoms in uncomplicated infection. However, it has limitations in understanding hospitalisations, complications, and the prevention of complications occurring in cases of severe infection, and mortality
- traditional RCTs for non-seasonal influenza viruses with high case fatality rates, or a novel influenza virus with pandemic potential, are by nature not ethical or feasible. No RCTs were carried out on severely ill patients as part of the licensure of these drugs and it would now not be possible to do this
- in the absence of appropriate RCT data on severe influenza, observational studies have important contributions to make to policy development
- a substantial volume of observational data was not considered in the Cochrane Review, including evidence of the ability of NAIs to stop the progression of severe cases of H5N1 or pandemic H1N1 infection.

It is essential that physicians treating severely unwell patients in any setting are not deterred from prescribing NAI drugs as a result of confusion over efficacy. This is especially true for patients hospitalised with proven or suspected influenza.

Prescribing considerations for healthcare professionals

Influenza management is a complex and evolving area. Early specialist advice from a clinical virologist or local microbiologist is recommended for the management of patients hospitalised with influenza. Further information is available in PHE's clinical guidance on the use of NAIs for the treatment and prophylaxis of influenza.[xii,xiii]

NICE guidance[xiv] should be considered by all clinicians (primary and secondary care).

GPs and primary care

- the grey list, which is included within the drug tariff, restricts GPs to only prescribing antiviral medicines to specified people who are listed in the clinical 'at risk' groups
- GPs have the discretion to prescribe antiviral medicines for people who may not be in the specified at-risk groups but who they believe would suffer serious complications if not treated with an antiviral medicine
- GPs treating at-risk patients should not be deterred from prescribing what may be life-saving drugs as a result of confusion over efficacy
- GPs should note PHE's advice on treating patients with suspected influenza who may not be in an at-risk group but who are appreciably unwell, and may benefit from treatment with NAIs

Secondary care doctors

- clinicians in secondary care should use their clinical judgement to prescribe antiviral medicines, including for those patients not in the at-risk groups
- physicians treating severely unwell patients in any setting should not be deterred from prescribing what may be life-saving drugs as a result of confusion over efficacy; this is especially true for patients hospitalised with proven or suspected influenza
- any patient, even if not in an at-risk group, who is hospitalised with suspected influenza and appreciably unwell, may benefit from early treatment with NAIs

Regional microbiologists and virologists

- patients with suspected influenza who may benefit from NAIs should be treated as soon as possible with NAIs, as recommended in PHE and NICE guidance. Waiting for positive diagnostic confirmation should not delay treatment

Conclusion

The findings of the Cochrane Review 2014 on NAIs are similar to the 2010 and 2012 reviews, and add to the evidence base for the treatment of influenza in some situations. It is important to note that the conclusions of the 2014 review are limited due to the variation in outcomes, patient groups, and settings studied, and the type of evidence included.

Although there is no evidence to support a change to the recommended use of neuraminidase inhibitors, media reporting around the Cochrane Review 2014 publication suggested that antivirals are not effective for influenza. It is essential that physicians treating severely unwell patients in any setting are not deterred from prescribing what may be life-saving drugs as a result of confusion over efficacy in this situation; this is especially true for patients hospitalised with proven or suspected influenza.

Due to evidence that antivirals can be of benefit in patients with severe influenza, PHE continues to support the use of NAIs for patients with proven or suspected seasonal influenza who are in high-risk groups (as per NICE guidance) or who are considerably unwell, particularly those who are hospitalised even if not in a high-risk group. This position is consistent with that taken by the World Health Organization (WHO) and national public health organisations such as the USA's Centers for Disease Control and Prevention (CDC).

Endnotes

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