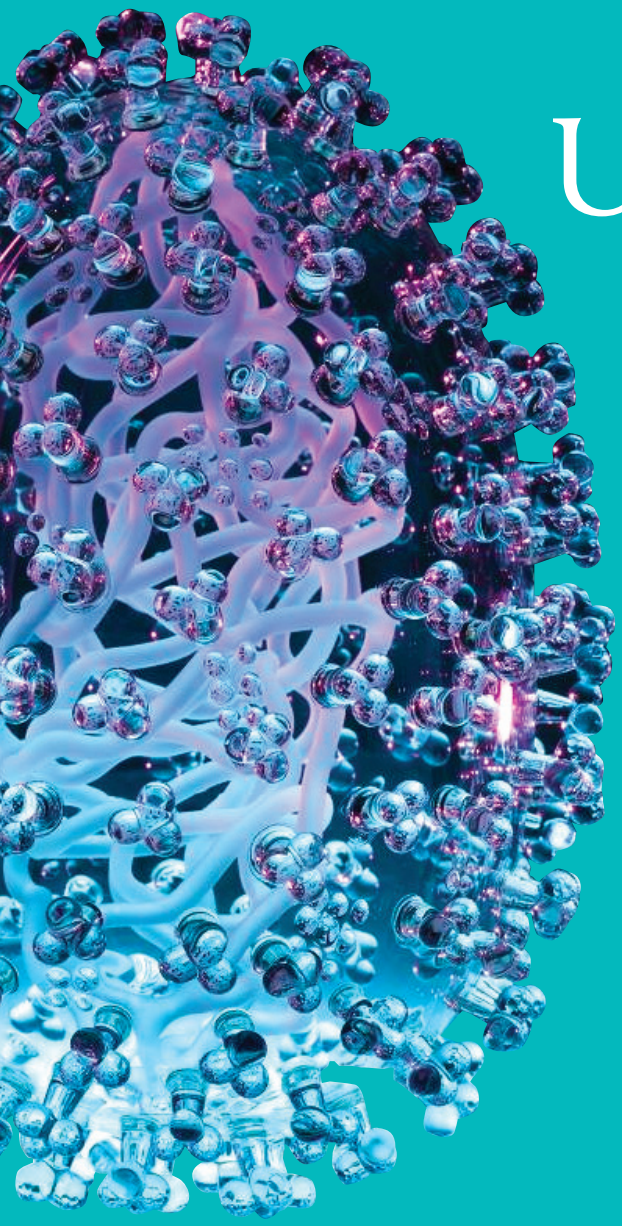

Use of neuraminidase inhibitors in *influenza*

October 2015

Image: Swine Flu virus Sculpture
Luke Jerram/Wellcome Images

wellcome trust

The Academy of Medical Sciences

Use of Neuraminidase Inhibitors in Influenza

Contents

1. Summary

Background

- Pandemic influenza tops the UK's National Risk Register due to the probability of a pandemic occurring and the social and economic disruption that could result from an influenza strain causing severe disease. The principal class of antivirals licensed for the treatment and prophylaxis of seasonal and pandemic influenza are neuraminidase inhibitors (NAIs), specifically oseltamivir (trade name: Tamiflu) and zanamivir (trade name: Relenza).
- Questions have been raised for some years about the efficacy and effectiveness of these NAIs and whether this justifies their being part of the UK government's response to influenza, and particularly whether the government is justified in stockpiling them. The Cochrane Collaboration's publication, in April 2014, of meta-analyses of randomised controlled trials (RCTs) of the use of oseltamivir and zanamivir during seasonal influenza, in part reactivated this debate. Three further publications of analyses of the use of NAIs for treatment and prophylaxis, which use data from RCTs conducted during seasonal influenza outbreaks and observational data collected during the 2009 H1N1 pandemic, have added to the evidence base and debate.
- In response to a request from the UK Department of Health, a small, **independent steering group** was established by the Academy of Medical Sciences and the Wellcome Trust to provide commentary on the implications of these new analyses, consider the pipeline for new treatments for influenza, and identify research priorities. The steering group was informed by a **one-day workshop** held in February 2015 and attended by the authors of the recent key studies as well as a range of individuals from clinical disciplines, public health, virology, industry and research funders.

Commentary on the recent publications

- Taking into account the strengths and limitations of the analyses of the efficacy, effectiveness and side-effects of NAIs, the steering group reached the following conclusions about the treatment of influenza with NAIs:
  - For **seasonal influenza** there is good evidence from RCTs that NAIs reduce the duration of symptoms – by 14–17 hours depending on the NAI. This is a relatively small benefit in a condition that is usually self-limiting and which only rarely leads to serious complications. The evidence therefore does not support the routine use of NAIs for the treatment of patients with seasonal influenza who are not severely ill. However, should a circulating pandemic or seasonal strain result in greater prevalence of infection or severity of symptoms, the routine use of NAIs for all patients with influenza might become advisable.
  - The evidence from the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) consortium's meta-analysis of observational studies conducted during the 2009 H1N1 pandemic shows that deaths in hospitalised patients reduced when NAIs were used, and the steering group considers that this supports the use of NAIs to treat **influenza in patients who require hospitalisation**.

- The current guidance recommends that if NAIs are to be used, treatment should commence within 48 hours of the first onset of symptoms. This is supported by the observational data from hospitalised patients collected by the PRIDE study, where the benefit of **treatment outside 48 hours of the onset of symptoms** is limited to cases of severely ill patients requiring admission to an intensive care unit (ICU). While the importance of initiating treatment as early as possible in those who do go on to develop severe disease is clear from these results, use of treatment in other scenarios must rely on clinical judgement, particularly because identifying these patients within 48 hours is not always possible. The steering group also notes that issues such as strain variation may affect the period of effectiveness.
- The current observational evidence supports the **treatment of pregnant women who are hospitalised** with influenza. There is a lack of evidence to guide decisions on NAI treatment for **other high-risk groups and children**. The steering group recognises that clinicians will need to balance the risks, such as nausea and vomiting, and benefits in choosing whether or not to recommend treatment to high-risk patients or children.

- There is a paucity of applicable evidence from the recent studies to inform a single approach for **prophylaxis in care homes**. These decisions must therefore be made on a case-by-case basis using clinical judgement and be based on the severity of the outbreak. There is both observational and RCT evidence to support the use of NAIs for **prophylaxis of influenza in individuals and households**. However, whether NAIs should be used for prophylaxis in individuals or households must take into account other factors, such as: the virulence of the circulating strain; cost-effectiveness; distribution; and the risk of resistance.
- Conclusions based on seasonal influenza cannot simply be extrapolated to an epidemic or pandemic situation. **The steering group stresses that if future outbreaks of influenza are more virulent or show greater incidence of complications and death than during the period when this evidence was collected, then the treatment of larger numbers of the population with NAIs may be justified.**
- Although **observational data** are generally at higher risk of bias than RCTs, the steering group does not support the assumption that observational data are invariably of less use than data from RCTs. RCTs will normally be better at determining efficacy, while observational data can better reflect the effectiveness of an intervention in usual care and identify rarer outcomes. In formulating policy and guidance it can be appropriate to use observational data, particularly when data from large, pragmatic RCTs are not available.
- The steering group does not consider it is appropriate to dismiss the studies from the Multiparty Group for Advice on Science (MUGAS) and PRIDE on the basis of their funding source. The authors of the studies and the company that supported them have been transparent about the arm's-length basis of these funding arrangements.
- This report considers a number of other issues that have provoked debate about the recent publications, including the quality of the evidence, the relevance of the underpinning data, the mechanisms of action of the NAIs, and data transparency.

Pipeline of new drugs and resistance

- The steering group notes that **resistance** to NAIs did not become a significant clinical issue in the 2009 H1N1 pandemic. However, present problems with bacterial resistance to antimicrobials highlight the potential outcome of unrestricted prescribing. There are alternatives to NAIs in the **development pipeline** and it is important that these are progressed in order to provide alternatives to NAIs if resistance becomes a significant clinical issue, and for use in combination with NAIs to limit the development of resistance to them.

Research priorities

- The failure to conduct RCTs in the 2009 H1N1 pandemic has contributed to the current weaknesses in the evidence base and the uncertainty facing clinicians. The steering group is sympathetic to the challenges that RCTs would raise for clinicians and patients in an epidemic or a pandemic scenario. However, subject to ethical and regulatory approval, the steering group concludes that conducting **RCTs of NAI use in hospitalised patients and in high-risk groups** in an epidemic or a pandemic is a high priority. It is essential that steps are taken now to put in place **pre-agreed protocols** and the research infrastructure for new high-quality and adequately powered RCTs, including those using novel approaches. Scenario planning and exercises for pandemics should include an assessment of the ability to activate these protocols immediately at the onset of a new epidemic or pandemic.
- Additional research to address current uncertainties should focus on: NAI treatment in primary care; prophylaxis (including cost-effectiveness and distribution methods); prospective observational studies of patients at risk of poor outcomes; pharmacokinetics-pharmacodynamics studies to improve understanding of the effective dose of NAIs; more accurately defining the time window for effective NAI treatment; improving understanding of which patients are at high risk of poor outcomes from an influenza infection; evaluations of cost-effectiveness; and health services research (for example on the implementation of public health measures and the behaviour of healthcare professionals). Where appropriate, pre-agreed protocols should be in place for this research too.

Preparedness

- There is clear evidence that NAIs reduce symptom duration, which may reduce the spread of influenza as well as its impact on individuals and the population (eg by reducing absence from work and the impact on carers). The evidence base comes mainly from a relatively mild pandemic in 2009 where hospitalisations and deaths were rare. At the outset of an outbreak only limited information may be available to predict who is likely to become severely ill. In a mild outbreak the number of people that will need to be treated to have a benefit will be considerable. The number that will need to be provided with prophylaxis to prevent a serious case is likely to be substantially larger. However, the more severe the pandemic (in terms of virulence and individual symptoms), the greater the likelihood of benefit to the population from the use of NAIs.
- Decisions about the use and stockpiling of antivirals are based on a range of considerations, including economic (cost-effectiveness), public health, political and ethical factors as well as the scientific evidence that is considered here. This report sets out the ways in which the scientific evidence base should be strengthened. However, the government will always have to make difficult policy decisions based on incomplete evidence and in the face of competing priorities.

2. Introduction

Pandemic influenza continues to represent the most significant civil emergency risk to the UK – above terrorist activity or natural disasters – due to the probability of a pandemic occurring and the social and economic disruption that could occur if an influenza strain were to cause widespread or severe disease[1]. At the launch of the UK Influenza Pandemic Preparedness Strategy 2011, the UK was recognised by the World Health Organization as one of the best-prepared countries for dealing with pandemic influenza[2]. The strategy includes a stockpile of both oseltamivir and zanamivir to ensure the UK's response "can be as flexible and resilient as possible, particularly against the risk of a pandemic virus strain developing resistance to oseltamivir"[3].

The 2009 H1N1 influenza pandemic fortunately caused less severe illness than initially feared, but nevertheless served to illustrate the need for flexibility of services in responding to a pandemic. At the workshop the steering group heard that the NHS was faced with increased demand for services at all levels, from primary care to intensive care, with a marked disruptive effect on the provision of routine services in many hospitals. Seasonal influenza generally presents much less of a threat, but is nonetheless recognised as a cause of excess mortality and a burden on the NHS, with estimates indicating around 8,000 influenza-attributable deaths per year[4]. The key definitions used in this report in relation to different types of influenza outbreak are contained in Box 1.

A combination of public health measures, antiviral medications and vaccines may mitigate the consequences of seasonal and pandemic influenza, and it is important that these interventions are based on evidence regarding the nature of the virus and the effectiveness of the intervention. The principal class of antivirals currently licensed for the treatment and prophylaxis of seasonal and pandemic influenza are neuraminidase inhibitors (NAIs).

During the 2009 H1N1 pandemic countries took different approaches to the use of antiviral NAIs[5]. Most countries used NAIs to target 'at-risk' patients. However, in Japan, for example, early treatment with NAIs was widespread in patients presenting with clinical illness, and the country had the lowest fatality rate of any developed nation[6]. Although a similar 'treat all' approach was adopted in the UK, the use of NAIs was lower in practice.

[1] Cabinet Office. National Risk Register of Civil Emergencies: 2015 edition. London: Cabinet Office; 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/419549/20150331_2015-NRR-WA_Final.pdf [accessed 29 July 2015].
[2] https://www.gov.uk/government/news/uk-is-amongst-the-best-prepared-in-the-world-for-a-pandemic [accessed 6 August 2015].
[3] Department of Health. UK Influenza Pandemic Preparedness Strategy 2011. London: Department of Health; 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213717/dh_131040.pdf [accessed 29 July 2015]. See page 41.
[4] Green *et al*. Mortality Attributable to Influenza in England and Wales Prior to, during and after the 2009 Pandemic. PLoS ONE 2014;8(12). http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0079360#s3 [accessed 6 August 2015]
[5] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.
[6] Shobayashi T. Japan's actions to combat pandemic influenza (A/H1N1). JMAJ 2011;54(5):284–89.

Between 2006 and 2013 the UK government spent £424 million stockpiling the NAI oseltamivir (trade name: Tamiflu) and a further £136 million stockpiling the alternative NAI zanamivir (trade name: Relenza) as a precautionary response to the threat of a highly virulent H5N1 pandemic[7]. Following the publication of the April 2014 Cochrane Collaboration report into the effectiveness of oseltamivir, there have been calls on the government to reconsider this stockpile as part of its pandemic influenza strategy[8].

The steering group recognises that decisions about the use of antivirals (including their stockpiling) are based on a range of considerations, including economic, public health, political, ethical and scientific factors. This report considers some of the scientific aspects of these decisions, which are an important determinant of government policy.

Box 1. Definitions

There are not universally agreed definitions for the key terms relating to influenza outbreaks. This report uses the terms 'seasonal' and 'pandemic' influenza, which the steering group has defined as follows[9]:

Seasonal influenza

Seasonal influenza viruses derive from pandemic viruses and circulate from year to year, causing disease, generally until the next pandemic virus occurs. In temperate climates disease tends to occur seasonally in the winter months, spreading from person to person. A seasonal influenza outbreak may be described as an epidemic when the number of people infected clearly rises beyond average expected levels in a country or region. Seasonal influenza viruses evolve continuously, and people can get infected multiple times with related viruses.

Pandemic influenza

Pandemics are normally caused by infection with a new virus, formed by genetic re-assortment between human and animal (often avian) influenza viruses which has the ability to infect and be transmitted between humans. Pandemics occur when most of the population have no immunity to the new virus, and are declared when the number of people infected clearly exceeds the expected levels globally, or when infection occurs across many countries at the same time. Some definitions of 'pandemic' require the infection to be severe[10]. However, in this report the steering group assumes that pandemics can involve severe or mild infection in individuals and considers the implications of variations in severity.

[7] House of Commons Committee of Public Accounts. Access to Clinical Trial Data and the Stockpiling of Tamiflu. London: The Stationery Office; 2014. http://www.publications.parliament.uk/pa/cm201314/cmselect/cmpubacc/295/295.pdf [accessed 29 July 2015].
[8] Jefferson T *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (review). The Cochrane Library 2014a;4. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/pdf [accessed 29 July 2015].
[9] World Health Organization. Influenza Virus Infections in Humans. World Health Organization 2014. http://www.who.int/influenza/human_animal_interface/virology_laboratories_and_vaccines/influenza_virus_infections_humans_feb14.pdf?ua=1 [accessed 29 July 2015].
[10] Morens D, Folkers G, Fauci A. What is a pandemic? J Infect Dis 2009;200 (7):1018–1021.

Terms of reference and conduct of this review

Given the debate about the implications of recent studies relevant to the use of NAIs, the UK Department of Health approached the Wellcome Trust and the Academy of Medical Sciences to convene a group of independent experts to review analyses of NAI use, in particular the two Cochrane meta-analyses that had been published in April 2014[11,12], the findings of the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) consortium that had been published in May 2014[13], and the Multiparty Group for Advice on Science (MUGAS) study that was expected to be published during the course of the review[14]. The aim of the Academy of Medical Sciences and the Wellcome Trust was to provide a joint, independent commentary on the results of the new studies and to interpret major recent contributions to the evidence base and their implications for treatment and prophylaxis in seasonal and pandemic influenza – but not to develop treatment guidelines. In addition, the two organisations decided to consider implications of the use of antiviral agents for the development of antiviral resistance and the development of new antivirals, and to identify research priorities and improvements needed in research methods.

The two organisations established a small steering group of experts (listed in Annex 1) who had not been involved in the publications being considered. While the Department of Health was consulted on the terms of reference for the review, its staff were not invited to approve them, nor did it approve the membership of the group. Potential conflicts of interest were declared at the first meeting and are outlined in Annex 1. The steering group defined and agreed the terms of reference, which included reviewing the latest analyses and their implications for the use of NAIs in scenarios that had been identified by the Department of Health (see Box 2).

Box 2. Terms of reference for the review

- Review the scientific evidence (primarily from recent systematic reviews and large cohort study reports) to determine what level of support there is for the use of existing antivirals in response to seasonal and pandemic influenza, specifically for:
  - treatment for individuals with underlying health conditions that predispose them to complications of influenza (including pregnant women) who develop influenza
  - treatment for previously healthy people who develop severe influenza
  - treatment for any previously healthy people with influenza that is not (currently) severe ('treat all' approach)
  - commencing treatment in severely ill individuals more than 48 hours after the onset of symptoms
  - prophylaxis.
- Consider the development and implications of resistance, including the development of new antivirals and new treatments.
- Identify research priorities and any improvements in methodologies that will support the treatment and prophylaxis of influenza.

[11] Jefferson T *et al*. Oseltamivir for influenza in adults in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014b;348. http://www.bmj.com/content/348/bmj.g2545 [accessed 29 July 2015].
[12] Heneghan CJ *et al*. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014;348. http://www.bmj.com/content/348/bmj.g2547 [accessed 29 July 2015].
[13] Muthuri SG *et al.* Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.
[14] Dobson J *et al*. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015;385(9979):1729–37. http://dx.doi.org/10.1016/S0140-6736(14)62449-1 [accessed 29 July 2015].

The steering group invited participants – selected on the basis of their direct interest or relevant expertise in the topic – to attend an evidence-gathering workshop held on 24 February 2015 at the Wellcome Trust in London (Annex 2 outlines the agenda and lists the attendees). The aim was to achieve representation from the authors of the recent key studies as well as from a range of individuals from relevant clinical disciplines (eg general practice and intensive care), public health, virology, industry and research funders. The steering group is very grateful to all those who participated in the workshop, particularly to the authors of the key studies who presented their research and provided written summaries that were circulated in advance[15]. Attendees were invited to provide written comments after the meeting. Roche, the manufacturer of oseltamivir, submitted a summary of its detailed analysis of the 2014 Cochrane review, based on its report previously published on the Cochrane Collaboration website. Detailed comments were also received from Professor Heneghan (Director, Centre for Evidence-Based Medicine, University of Oxford), author of the Cochrane review[16].

The report was approved for publication by the Council of the Academy of Medical Sciences and by the Wellcome Trust. The conclusions of the report were not discussed with the Department of Health before the report was finalised.

Current influenza guidelines

A summary of the current UK guidance (and guidance from other countries and international bodies) as it relates to different scenarios is presented in Annex 3; the UK Influenza Pandemic Preparedness Strategy 2011 describes nonmedical interventions that may be required[17].

At the evidence-gathering workshop the steering group heard that GPs are unclear about when they should treat individuals with antivirals in different scenarios, and which patients constitute high-risk groups and why. For example, the issue of guidance regarding the use of NAIs for prophylaxis in nursing homes has been met with a degree of scepticism because of uncertainty about how the current evidence base relates to the guidance[18,19,20].

[15] Academy of Medical Sciences and the Wellcome Trust. Supplementary material: use of neuraminidase inhibitors in influenza. London: Academy of Medical Sciences and the Wellcome Trust; 2015. http://www.acmedsci.ac.uk/snip/uploads/560d197898581.pdf [accessed 1 October 2015].
[16] Roche response to the Cochrane review: http://editorial-unit.cochrane.org/cochrane-review-neuraminidase-inhibitors-influenza [accessed 29 July 2015].
[17] Department of Health. UK Influenza Pandemic Preparedness Strategy 2011. London: Department of Health; 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213717/dh_131040.pdf [accessed 29 July 2015].
[18] Cohen D. GPs are told to treat with scepticism advice on anti-flu drugs from Public Health England. BMJ 2015;350. http://www.bmj.com/content/350/bmj.h258 [accessed 29 July 2015].
[19] Macdonald H. Should I prescribe anti-virals to prevent flu for nursing home patients? BMJ Today 2015 21 January. http://blogs.bmj.com/bmj/2015/01/21/the-bmj-today-should-i-prescribe-anti-virals-to-prevent-flu-for-nursing-home-patients/ [accessed 29 July 2015].
[20] McCartney M. Margaret McCartney: Don't be bullied into prescribing Tamiflu. BMJ 2015;350. http://www.bmj.com/content/350/bmj.h417 [accessed 29 July 2015].

3. Studies considered in this report

In developing its conclusions, the steering group considered the following key studies that were published in 2014 and 2015:

- Meta-analyses considering treatment and prophylaxis of seasonal influenza with neuraminidase inhibitors (NAIs):
  - at the level of each trial (the Cochrane review [Jefferson *et al*., 2014a[21]], which has also been published as two separate papers on oseltamivir [Jefferson *et al*., 2014b[22]] and zanamivir [Heneghan *et al*., 2014[23]])
  - at the level of individual patient data (the Multiparty Group for Advice on Science [MUGAS] review [Dobson *et al*., 2015[24]]).

  These meta-analyses are based on almost the same set of trials. The MUGAS review incorporates all trials of oseltamivir treatment in adults included in the Cochrane review, plus one additional trial.
- The findings of the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) consortium, which gathered retrospective observational data on the use of NAIs in the 2009 H1N1 pandemic (Muthuri *et al*., 2014[25]).
- A meta-analysis of randomised and observational study data (Okoli *et al*., 2014[26]) considering the prophylactic use of NAIs.

Tables 1 and 2 summarise the approaches and main findings of these key studies for the treatment and prophylaxis of influenza respectively. The authors of the included studies provided summaries of their studies in advance of the evidence-gathering workshop, which are available alongside this report[27].

Statistical terms used in this report are defined in Annex 4.

There is ongoing debate about the different methodologies employed to assess the evidence of medical interventions and the implications of these methodologies on the interpretation of evidence informing policy and guidance. The evidence-gathering workshop demonstrated that this debate is currently occurring around the use of NAIs. The steering group has considered the strengths and limitations of the studies included in this review; these strengths and weaknesses are discussed in the following section.

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[21] Jefferson T *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (review). The Cochrane Library 2014a;4. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/pdf [accessed 29 July 2015].
[22] Jefferson T *et al*. Oseltamivir for influenza in adults in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014b;348. http://www.bmj.com/content/348/bmj.g2545 [accessed 29 July 2015].
[23] Heneghan CJ *et al*. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014;348. http://www.bmj.com/content/348/bmj.g2547 [accessed 29 July 2015].
[24] Dobson J *et al*. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015;385(9979):1729–37. http://dx.doi.org/10.1016/S0140-6736(14)62449-1 [accessed 29 July 2015].
[25] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.
[26] Okoli GN *et al*. Use of neuraminidase inhibitors for rapid containment of influenza: a systematic review and meta-analysis of individual and household transmission studies. PLoS ONE 2014;9(12). http://www.ncbi.nlm.nih.gov/pubmed/25490762 [accessed 29 July 2015].
[27] Academy of Medical Sciences and the Wellcome Trust. Supplementary material: use of neuraminidase inhibitors in influenza. London: Academy of Medical Sciences and the Wellcome Trust; 2015. http://www.acmedsci.ac.uk/snip/uploads/560d197898581.pdf [accessed 1 October 2015].

Table 1. Summary of studies considered: treatment of influenza

	Jefferson *et al*., 2014a (Cochrane review)	Muthuri *et al*., 2014 (PRIDE)	Dobson *et al*., 2015 (MUGAS)
Pandemic or seasonal	Seasonal	Pandemic H1N1	Seasonal
Type of study	Meta-analysis of clinical study reports of randomised controlled trials (RCTs) of oseltamivir and zanamivir	Observational data of hospitalised patients during the 2009 pandemic	Individual patient data meta-analysis of RCTs of oseltamivir in adults
Funding source	National Institute for Health Research (NIHR) Health Technology Assessment programme	Roche unrestricted educational grant	Multiparty Group for Advice on Science Foundation through an unrestricted Roche grant
Size of dataset	For oseltamivir 6,574 in treatment trials For zanamivir 7,678 in treatment trials	29,234 patients	4,328 patients
Primary outcome measure(s)	1. Symptom relief (mean time to first alleviation of symptoms) 2. Hospitalisation and complications 3. Harms	Mortality	1. Median time to alleviation of all symptoms (alleviation deemed to arise when all symptoms scored as absent or mild and remained so for at least 21.5 hours) 2. Lower respiratory tract complications more than 48 hours after randomisation requiring antibiotics
Secondary outcome measure(s)	1. Symptom relapse after finishing treatment 2. Drug resistance 3. Viral excretion 4. Mortality		1. Admission to hospital for any cause 2. Death 3. All adverse events

Table 2. Summary of studies considered: prophylaxis of influenza

	Jefferson *et al*., 2014a (Cochrane review)	Okoli *et al*., 2014
Pandemic or seasonal	Seasonal	Seasonal and pandemic (though only seasonal studies were available for zanamivir)
Type of study	Meta-analysis of clinical study reports of RCTs of oseltamivir and zanamivir	Meta-analysis of RCTs and observational data
Funding source	National Institute for Health Research (NIHR) Health Technology Assessment programme	World Health Organization
Size of data set	For oseltamivir 3,049 in prophylaxis For zanamivir 6,950 in prophylaxis	Nine RCTs (10,532 participants in total) and eight observational studies (8,740 participants in total) For oseltamivir this included four RCTs and seven observational studies; for zanamivir this included five RCTs
Primary outcome measure(s)	1. Influenza (symptomatic and asymptomatic, always with laboratory confirmation) and influenza-like illness (ILI) 2. Hospitalisation and complications 3. Interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts) 4. Harms	Community transmission (epidemiologically linked cases in settings other than hospitals, care/nursing homes, boarding schools and places of detention)
Secondary outcome measure(s)	1. Drug resistance 2. Viral eradication 3. Mortality	

4. Strengths and limitations of the studies considered

This section considers general issues around the strengths and limitations of the studies the steering group considered. More specific issues, such as trial design, that relate to how the data were interpreted in the context of the terms of reference are discussed in the relevant part of the 'Synthesis of evidence' section.

Quality of evidence

The evidence for the efficacy of using neuraminidase inhibitors (NAIs) in the treatment or prophylaxis of influenza comes from two main sources: randomised controlled trials (RCTs) and observational studies. The meta-analyses of RCTs focus on the treatment of seasonal influenza in a community setting, whereas the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) meta-analysis[28] is an observational study based on data from hospitalised patients.

It is important to consider the strengths and limitations of these different methodologies (see Annex 5) when they are to inform guidance and policy. Evidence from RCTs, including their meta-analysis, is seen as the gold standard for evidence of efficacy of interventions, since randomisation attempts to ensure that both known and unknown confounding factors are evenly distributed between groups and blinding minimises the risk of bias[29]. Observational data may provide evidence that better reflects actual practice (the 'real world' effectiveness) and may identify rarer but important outcomes. However, conclusions about treatment effects from nonrandomised, unblinded studies are generally at higher risk of bias[30,31]. The relative weight that is given to these different sources of data should therefore reflect the question being asked[32].

The steering group does not support the assumption that observational data are invariably of less use than data from RCTs. RCTs will normally be better at determining efficacy, while observational data can better reflect the effectiveness of an intervention in usual care and identify rarer outcomes. In formulating policy and guidance it can be appropriate to use observational data, particularly when data from large, pragmatic RCTs are not available.

A new Academy of Medical Sciences project is examining the strengths and limitations of different sources of evidence in more detail[33].

[28] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.
[29] Concorto J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. New Eng J Med 2000;342(25):1887–92.
[30] Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ1998;317:1185–90.
[31] Guyatt GH *et al*. What is 'quality of evidence' and why is it important to clinicians? BMJ 2008;336:995–8.
[32] Boaz A, Ashby D. Fit for Purpose? Assessing research quality for evidence based policy and practice. London: ESRC UK Centre for Evidence Based Policy and Practice; 2003. http://www.kcl.ac.uk/sspp/departments/politicaleconomy/research/cep/pubs/papers/paper-11.aspx [accessed 29 July 2015].
[33] http://www.acmedsci.ac.uk/policy/policy-projects/how-does-society-use-evidence-to-judge-the-risks-and-benefits-of-medicines/ [accessed 6 August 2015].

Individual patient data and study level analyses

The Cochrane[34] and Multiparty Group for Advice on Science (MUGAS)[35] meta-analyses are based on data sets from almost the same set of RCTs. Both analyses use the clinical study reports rather than the publications of the studies to allow fully independent analysis and to ensure accurate representation of the data. Both analyses reach broadly similar conclusions, particularly on the primary outcome of time to alleviation of symptoms. However, there is an important difference in approach, as the MUGAS analysis was conducted at the individual patient data level, whereas the Cochrane analysis was conducted at the study level. Subgroup analyses, effects of covariates and exploring correlations of various outcomes can only be done by using individual participant data (IPD) or specially requested analyses of individual studies[36,37]. However, many questions can be answered by reviews based on summary statistics from well-reported studies.

Lack of completeness of data

The datasets or studies included in a meta-analysis will impact on its applicability and quality. This had implications for a number of the analyses the steering group considered. For example, Muthuri *et al*. contacted 401 authors of existing studies for data (which included multiple authors relating to a single dataset). Of these, 128 replied, with 77 confirming willingness to take part. Some further contributions were lost due to difficulties such as lack of capacity or data-sharing restrictions. Muthuri *et al*. estimate that "in a worst case scenario, it is possible that less than 20% of potential sites contributed to this analysis"[38]. However, taking this into account, the study is still large and includes data from 29,234 people.

Conflicts of interest and transparency

The issue of investigators' conflicts of interest is a contemporary subject of debate, with some researchers, and parts of the scientific and popular media, suggesting that funding conflicts can affect treatment recommendations[39]. In its publication and at the workshop Professor Van-Tam (Professor of Health Protection, University of Nottingham), leader of the PRIDE study, made it clear that this study was funded through an unrestricted educational grant from F. Hoffmann-La Roche[40,41]. The terms of the grant meant that the company had no input into the project design, no access to any of the data, no role in analysis or data interpretation, no preview of the study results and no opportunity to preview or comment on any manuscripts arising from the work. A similar Roche unrestricted grant funded the MUGAS project[42,43]. The steering group does not consider it is appropriate to dismiss the findings of MUGAS and PRIDE simply on the basis of their funding source and notes that there has

[34] Jefferson T *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (review). The Cochrane Library 2014a;4. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/pdf [accessed 29 July 2015].
[35] Dobson J *et al*. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015;385(9979):1729–37. http://dx.doi.org/10.1016/S0140-6736(14)62449-1 [accessed 29 July 2015].
[36] The Cochrane Individual Participant Data (IPD) Meta-analysis Methods Group's guidance on IPD meta-analyses is available here: http://ipdmamg.cochrane.org/about-ipd-meta-analyses [accessed 29 July 2015].
[37] Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002;25(1):76–97.
[38] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404. See page 403.
[39] Dunn AG *et al*. Financial conflicts of interest and conclusions about neuraminidase inhibitors for influenza: an analysis of systematic reviews. Ann Intern Med 2014;161(7): 513–18.
[40] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.
[41] http://www.nottingham.ac.uk/research/groups/healthprotection/projects/pride.aspx [accessed 5 August 2015]. See *Frequently asked questions: Who is funding this project?*
[42] Dobson J *et al*. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015;385(9979):1729–37. http://dx.doi.org/10.1016/S0140-6736(14)62449-1 [accessed 29 July 2015]. See page 1732.
[43] http://mugas.net/review-meeting-18-june-2013/support/ [accessed 5 August 2015].

been transparency about their funding. The steering group recognises that potential biases may also arise from other kinds of pressures that are equally or more pertinent to non-industry-funded research. For example, authors' approaches to particular research questions may also be influenced by the desire for prestige, profile and success in grant applications.

The availability of trial data for reanalysis beyond that presented in published manuscripts is a well-publicised issue and was discussed at the workshop. This issue is beyond the scope of this report, but the steering group welcomes the fact that some companies have established frameworks to make more data available to researchers and encourages further discussions across all trial stakeholders[44,45].

There was also a discussion at the workshop about the transparency of protocols. Core to Cochrane's approach is the development and availability for review of its protocols prior to conducting the main study. This avoids post hoc justification for selectively reporting analyses and findings that are favourable to a particular view. The Cochrane Collaboration also promotes open dialogue between the authors and other interested parties about the approach being taken. This approach is not adopted by all authors of meta-analyses, and it was noted at the evidence-gathering workshop that the MUGAS protocol was not made available prior to its main analysis.

[44] See for example, Clinical Study Data Request https://www.clinicalstudydatarequest.com/ [accessed 26 August 2015].
[45] Institute of Medicine. Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk. 2015. https://iom.nationalacademies.org/Reports/2015/Sharing-Clinical-Trial-Data.aspx [access 26 August 2015].

5. Synthesis of evidence and implications

Taking into account the strengths and limitations of the studies, the steering group has considered how the evidence from these studies relates to the different scenarios for treating influenza and its prophylaxis. Table 3 summarises each of the studies against the terms of reference. The following section considers the evidence from the studies examined and the steering group's conclusions about the implications of the data for each of the scenarios. It should be stressed throughout that if future outbreaks of influenza are more virulent or show greater incidence of complications and death than during the period when this evidence was collected, then the treatment of larger numbers of the population would need to be considered.

a) Treatment for any previously healthy people with influenza that is not (currently) severe ('treat all' approach)

Benefits of neuraminidase inhibitor (NAI) treatment in influenza that is not severe

In terms of the treatment of seasonal influenza with NAIs, the Cochrane and Multiparty Group for Advice on Science (MUGAS) meta-analyses differ in methodology and primary outcome measures. However, the two studies are based on almost the same set of trials[46], include similar numbers of patients in their primary analyses, and come to comparable estimates of efficacy with similar precision. In both studies NAI treatment reduces the time to alleviation of symptoms in patients with influenza-like illness (ILI) (Jefferson *et al.2014a*: oseltamivir improved the mean time to first alleviation of symptoms over the placebo by 16.8 hours [95% CI 8.4 hours to 25.1 hours], zanamivir by 14.4 hours [95% CI 9.4 hours to 19.4 hours]; Dobson *et al*.: oseltamivir improved the median time to alleviation of all symptoms over the placebo by 17.8 hours [95% CI 9.3 hours to 27.1 hours]).

Workshop participants discussed what they saw as the limitations of the commonly used 'time to first alleviation of symptoms' measure, which does not capture individuals whose symptoms return after a short period of apparent improvement. More generally, it was suggested that patient-focused outcomes that measure quality of life or time to return to usual activities/work could be a more useful outcome measure for considering the overall impact of interventions.

The Cochrane review found that oseltamivir made no significant difference to hospitalisation rate compared to placebo (Relative Risk (RR) 0.92 [95% CI 0.57 to 1.50]). In the MUGAS review the treatment of all patients with ILI (the intention to treat [ITT] population) also showed no statistically significant reduction in the subsequent all-cause hospitalisation of patients treated for non-severe influenza in the community (RR 0.61 [95% CI 0.36 to 1.03; p=0.066]: 25/2402 randomised to oseltamivir compared to 35/1926 randomised to placebo), but in the sub-group with confirmed influenza infection there was a 63% risk reduction (RR 0.37 [95% CI 0.17 to 0.81], 9/1591 patients randomised to oseltamivir compared to 22/1302 patients randomised to placebo). However, so few patients required hospital admission in the trials analysed that these results are hard to interpret.

[46] The Cochrane review was based on eight trials and the MUGAS review incorporated all the trials included in the Cochrane review, plus one additional trial. Some patients for whom no outcome data were available were excluded from the individual patient data analysis in the MUGAS review. In analyses of time to alleviation of symptoms the MUGAS review included a total of 2360 and 1904 patients randomised to oseltamivir and placebo respectively, compared to 2208 and 1746 patients respectively in the Cochrane review.

Treatment effect for confirmed influenza compared to influenza-like illness

The MUGAS study compared the response to NAIs in patients with confirmed influenza (ITTI population[47]) to the response in those with ILI (ITT population). The time to alleviation of all symptoms in the ITTI group was 25.2 hours shorter than the placebo (95% CI, 16.0 hours to 36.2 hours) compared to a reduction of 17.8 hours (95% CI 9.3 to 27.1) in the ITT group. Since current UK practice is not to test before administering NAIs, the ITT result is likely to be more indicative of the effectiveness of NAIs in routine care, although infection rates will vary between strains. In infectious disease research it is standard practice to consider both ITT and ITTI analysis. ITT analysis is considered more rigorous in minimising bias and usually gives more conservative estimates of efficacy[48]. However, ITTI analysis is relevant in the case of influenza since NAIs are not thought to be active against other respiratory viral infections (see the next section). The number of patients with ILI that is not influenza will vary from outbreak to outbreak, as will the ease with which influenza can be diagnosed without a specific test. This will affect the extent to which either the ITTI or ITT evidence is most applicable to normal clinical practice.

Mechanism of action of NAIs

The Cochrane review hypothesised that the action of NAIs may primarily be anti-pyretic and may modify the immune response or the functioning of the immune system rather than specifically acting on the influenza virus. A potential concern is that this could increase transmission, as people might feel better and socialise while still shedding the virus. The steering group notes that this hypothesis about the mode of action is not consistent with the ITTI/ITT data from the MUGAS review that indicate that NAIs confer greater benefit in patients with confirmed influenza rather than those with ILI. In addition, NAIs were based on rational design, and there is a body of preclinical data indicating that the NAIs specifically inhibit viral neuraminidase[49,50].

Potential side-effects of NAI treatment

It is important to consider the potential side-effects of treatment along with the benefits. The Cochrane meta-analysis found that compared to placebo, treatment of influenza with oseltamivir increased risks of nausea and vomiting, and use in prophylaxis increased risks of headache, renal events, nausea and psychiatric events. Patients receiving oseltamivir reported less diarrhoea than those receiving placebo and had fewer cardiac events. Patients receiving zanamivir experienced less nausea and vomiting than those receiving placebo, and no statistically significant difference in other side effects. In its comments on the Cochrane review, Roche agrees that the safety data indicate that around 10 per cent of patients experience vomiting, but disputes the methodology that found evidence of renal and neuropsychiatric effects[51]. Roche's comments are also consistent with the MUGAS review, which identified increased risks of nausea and vomiting, but no increased risk of neurological or psychiatric disorders.

[47] Some ITT analyses only consider participants in which there has been a confirmation of the infection – these are intention-to-treat-infected analyses (ITTI). In influenza reports an ITTI analysis would mean that influenza had been confirmed with laboratory testing.
[48] Gupta SK. Intention-to-treat concept: a review. Perspect Clin Res 2011;2(3), 109–12.
[49] Academy of Medical Sciences and the Wellcome Trust. Supplementary material: use of neuraminidase inhibitors in influenza. London: Academy of Medical Sciences and the Wellcome Trust; 2015. http://www.acmedsci.ac.uk/snip/uploads/560d197898581.pdf [accessed 1 October 2015].
[50] See the Roche response to the Cochrane review: http://editorial-unit.cochrane.org/cochrane-review-neuraminidase-inhibitors-influenza [accessed 29 July 2015].
[51] Ibid.

Balancing benefits and side-effects

In most cases of seasonal influenza patients experience an unpleasant but self-limiting illness with a low risk of complications. The evidence is compelling that NAI use reduces the symptomatic period compared to a placebo. However, considering both the relatively short reduction in the symptomatic period and the evidence of increased risk of nausea and vomiting, the value of NAI treatment of previously healthy individuals with seasonal influenza that is not severe appears limited. At the workshop it was noted that the circumstances of some individuals, for example those needing to return to work and parents and other carers, may mean that a reduction in function-limiting symptoms of around 17 hours would be a significant benefit. In these cases the balance of benefit and harm at an individual level may be shifted in favour of treatment. Cost-effectiveness analyses related to the virulence and severity of symptoms of the circulating strain considering a societal perspective are needed to further inform such judgements.

The 2009 H1N1 pandemic was generally mild and, like seasonal influenza, was primarily a self-limiting illness with a low risk of complications[52]. However, pandemics vary in virulence and severity of symptoms; it is not possible to predict in advance how severe a future pandemic will be, and the time available to collect appropriate data and make informed decisions is limited. In a severe pandemic, where the risk of complications and death are higher than for mild influenza, the benefits of NAI treatment could increase relative to the side-effects. In addition, in a severe pandemic population factors are also likely to become a relevant consideration in deciding whether or not it is appropriate to treat individuals who are not currently severely ill. For example, the benefits of limiting time away from work may be considerable if a large proportion of the workforce are infected, particularly in key sectors such as transport, security and healthcare. Reducing the duration of infection may also reduce overall rates of transmission of the virus.

Conclusions from seasonal influenza cannot necessarily be extrapolated to a severe epidemic or pandemic, where the balance of benefits and side-effects is likely to be different. In a severe epidemic or pandemic setting it is therefore possible that routine use of NAIs might be recommended for patients with influenza who are not severely ill. Such a decision would have to take into account how infectious and severe the disease is. Benefit from antiviral agents may vary according to strain even in severe illness, and the benefit seen from the use of NAIs in mild influenza may not increase in proportion to the severity of the illness. Ideally, therefore, evidence should be generated in the relevant setting and from the infecting strain that the antiviral is intended to target. Given that pandemic strains are likely to be new and not previously researched, this presents a significant challenge in terms of gathering and analysing relevant data in a timely way to inform practice.

The steering group considers that the balance between the short duration of the alleviation of symptoms and the possibility of side-effects does not support the routine use of NAIs for the treatment of patients with seasonal influenza who are not severely ill. However, should the prevalence or severity of symptoms of influenza be greater than in the outbreaks analysed, the routine use of NAIs for all patients with influenza might become advisable.

[52] Donaldson LJ *et al*. (2009). Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 2009;339. http://www.bmj.com/content/339/bmj.b5213 [accessed 29 July 2015].

Table 3. Summary of findings of studies considered according to the terms of reference

	Jefferson *et al*., 2014a (Cochrane)[53], Jefferson *et al*. 2014b (BMJ)[54], Heneghan *et al*. 2014 (BMJ)[55]	Okoli *et al*., 2014[56]	Muthuri *et al*., 2014 (PRIDE)[57]	Dobson *et al*., 2015 (MUGAS)[58]
Pandemic or seasonal	Seasonal	Oseltamivir: seasonal and pandemic Zanamivir: seasonal	Pandemic H1N1	Seasonal
Previously healthy people with influenza that is not (currently) severe ('treat all' approach) [59]	Reduction in mean time to first alleviation of symptoms compared to placebo: Oseltamivir: 16.8 hours (95% CI 8.4 hours to 25.1 hours), p<0.0001 Zanamivir: 14.4 hours (9.4 hours to 19.4 hours), p<0.0001, with no statistically significant difference in symptom reduction whether influenza was confirmed or not	Does not address this issue	Does not address this issue as only hospitalised patients included	Reduction in median time to alleviation of all symptoms for oseltamivir treatment: All patients: intention to treat (ITT) population: 17.8 hours (95% CI 9.3 hours to 27.1 hours) Patients with confirmed influenza: intention to treat infected (ITTI) population): 25.2 hours (95% CI 16.0 hours to 36.2 hours)

[53] Jefferson T *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (review). The Cochrane Library 2014a;4. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/pdf [accessed 29 July 2015].
[54] Jefferson T *et al*. Oseltamivir for influenza in adults in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014b;348. http://www.bmj.com/content/348/bmj.g2545 [accessed 29 July 2015].
[55] Heneghan CJ *et al*. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014;348. http://www.bmj.com/content/348/bmj.g2547 [accessed 29 July 2015].
[56] Okoli GN *et al*. Use of neuraminidase inhibitors for rapid containment of influenza: a systematic review and meta-analysis of individual and household transmission studies. PLoS ONE 2014;9(12). http://www.ncbi.nlm.nih.gov/pubmed/25490762 [accessed 29 July 2015].
[57] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.
[58] Dobson J *et al*. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015;385(9979):1729–37. http://dx.doi.org/10.1016/S0140-6736(14)62449-1 [accessed 29 July 2015].
[59] The analyses of time to symptom alleviation in the Cochrane review and MUGAS study covers all participants in the trials included. These findings are therefore not specific to "previously healthy people". However, most of the studies included in the primary analyses include 'free living' adults. Although people with respiratory disease and some chronic cardiac conditions were eligible in one trial (MV15812), most of the trials included in the primary meta-analyses in these two studies excluded people with serious co-morbidities.

Previously healthy people with influenza that is not (currently) severe cont.	Oseltamivir made no significant difference to hospitalisation rate (Relative Risk (RR) 0.92 [95% CI 0.57 to 1.50]) Hospitalisations were not reported for zanamivir trials			No statistically significant difference was found in the ITT population in admission to hospital (RR 0.61 [95% CI 0.36 to 1.03]; p=0.066), although decreased admission rates were observed in the ITTI group (RR 0.37 [95% CI 0.17 to 0.81]; p=0.013)
Previously healthy people who develop severe influenza	Reduction in self-reported, non-verified pneumonia with oseltamivir (RR 0.55 [95% CI 0.33 to 0.90]). No studies reported radiologically confirmed pneumonia, but studies using more detailed diagnostic data than self-reporting found no significant difference in rates of pneumonia for those using oseltamivir compared to controls There was no statistically significant difference in the rates of either self-reported or radiologically confirmed pneumonia in patients using zanamivir compared to controls (RR 0.90 [95% CI 0.58 to 1.40] for self-reported; RR 1.02 [95% CI 0.35 to 3.02] for radiologically confirmed)	Does not address this issue	NAI treatment associated with lower mortality risk in all age hospitalised patients and adults after adjustment for steroid use, antibiotic use and treatment propensity score[60]: adjusted odds ratio (adjOR) for treatment at any time compared to none: All ages: 0.81 (95% CI 0.70 to 0.93; p=0.002) Influenza confirmed: 0.82 (95% CI 0.70 to 0.95; p=0.010) Adults: 0.75 (95% CI 0.64 to 0.87; p<0.001) Adults in critical care: 0.72 (95% CI 0.56 to 0.94; p=0.016) When children were stratified, mortality benefits were not statistically significant: Children under 16: 0.82 (95% CI 0.58 to 1.17; p=0.28) Children in critical care: 0.70 (95% CI 0.42 to 1.16; p=0.17)	In the intention to treat infected population, reduced rates of lower respiratory tract complications: RR 0.56 (95% CI 0.42 to 0.75; p<0.001) This benefit was attenuated in the whole ITT population (RR 0.62 [95% CI 0.49 to 0.79]) and no statistically significant effect was found in the intention to treat not infected population (RR 0.82 [95% CI 0.53 to 1.26])

[60] Muthuri *et al.* included data for patients admitted to hospital with laboratory confirmed or clinically diagnosed pandemic influenza A H1N1pdm09 virus. These findings are therefore not specific to 'previously healthy people' and 38% of patients were recorded as having "any comorbidity".

Commencing treatment in severely ill individuals more than 48 hours after onset of symptoms	Does not address this issue	Does not address this issue	Where treatment was started more than 48 hours after symptom onset, across all patients there was no statistically significant difference in mortality compared to no treatment: adjOR 1.20 (95% CI 0.93 to 1.54; p=0.15) The only sub-group of patients with a statistically significant reduction in mortality from treatment even after 48 hours were adult patients admitted to critical care: AdjOR 0.65 (95% CI 0.46 to 0.93; p=0.018)	Does not address this issue
Individuals predisposed to complications of influenza (including pregnant women, older patients and those with underlying health problems)	Does not address this issue	Does not address this issue	Treatment reduced mortality in pregnant women: adjOR 0.46 (95% CI 0.23 to 0.89; p=0.022) at any time compared to none, but if treatment was later than 48 hours after symptom onset, there was no statistically significant difference in mortality compared to receiving no treatment: adjOR 0.70 (95% CI 0.24 to 2.06; p=0.51)	Those aged 65 years or over showed no statistically significant difference in duration of symptoms (17. 4 hours [95% CI 49.8 hours reduction to 15.6 hours increase]) 'High risk' patients were defined as those with chronic airways disease or in a chronic illness trial or aged older than 65 years. This age group was then extended to older than 50 years. Oseltamivir showed no statistically significant reduction in symptom duration in either group: patients older than 65 years: symptom reduction of 11.2 hours [95% CI 37.5 hours less to 18.2 hours more]); patients aged 50 or over: symptom reduction of 18.1 hours [95% CI 39.7 hours less to 5.1 hours more])

Side effects of treatment	Oseltamivir was associated with increased nausea (RR 1.57 [95% CI 1.14 to 2.15]; Number Needed to Harm (NNTH)=28)) and vomiting (RR 2.49 [95% CI 1.75 to 3.38]; NNTH=22) It was associated with fewer reports of diarrhoea (RR 0.67 [95% CI 0.46 to 0.98]) and general cardiac effects in adults (RR 0.49 [95% CI 0.25 to 0.97]), although one trial suggested a 4% increased risk of QT prolongation (95% CI 0.7% to 7.3%; NNTH=25) Oseltamivir had no significant increase in risk of psychiatric adverse effects overall, however there was a dose-response effect in two trials Oseltamivir was associated with increased vomiting in children (RR 1.70 [95% CI 1.23 to 2.35]; NNTH=19) Zanamivir was not associated with an increased risk of reported adverse events (RR 0.86 [95% CI 0.49 to 1.50]). There was a decreased rate of nausea and vomiting (RR 0.60 [95% CI 0.39 to 0.94]) and no significant difference in the rate of diarrhoea (RR 0.87 [95% CI 0.66 to 1.14])	Does not address this issue	Does not address this issue	Increased risk of nausea (RR 1.60 [95%CI 1.29 to 1.99]) and vomiting (RR 2.43 [95% CI 1.83 to 3.23]) with oseltamivir compared to placebo Fewer reports of diarrhoea (RR 0.75 [95% CI 0.60 to 0.95]) and cardiac disorders (RR 0.49 [95% CI 0.25 to 0.98]) No effect on neurological (RR 1.00 [95% CI 0.76 to 1.30]) or psychological disorders (RR 0.62 [95% CI 0.26 to 1.45])

Side effects of treatment cont.	With zanamivir there was no increased risk of adverse events in children, but data were sparse			
Prophylaxis	Reduced the likelihood of symptomatic influenza in individuals: oseltamivir RR 0.45 (95% CI 0.30 to 0.67; number needed to benefit (NNTB)=33) zanamivir RR 0.39 (95% CI 0.22 to 0.70; NNTB=51) Reduced the likelihood of symptomatic influenza in households: oseltamivir RR 0.20 (95% CI 0.09 to 0.44; NNTB=7) zanamivir RR 0.33 (95% CI 0.18 to 0.58; NNTB=7)	Reduced the likelihood of laboratory confirmed influenza in individuals (pre- or post-exposure): oseltamivir odds ratio (OR) 0.11 (95% CI 0.06 to 0.20; p<0.001) zanamivir OR 0.23 (95% CI 0.16 to 0.35; p<0.001) Reduced the likelihood of laboratory confirmed influenza in households: oseltamivir OR 0.23 (95% CI 0.09 to 0.59; p<0.002) zanamivir OR 0.18 (95% CI 0.10 to 0.31; p<0.001)	Does not address this issue	Does not address this issue
Side effects of prophylaxis	Oseltamivir was associated with statistically significant risk of headache (RR 1.18 [95% CI 1.05 to 1.33]; NNTH=32), nausea (RR 1.96 [95% CI 1.20 to 3.20]; NNTH=25) and psychiatric events (RR 1.80 [95% CI 1.05 to 3.08]; NNTH=94) There was no significant increase in adverse effects observed in zanamivir prophylaxis trials, but no figures are reported	Does not address this issue	Does not address this issue	Does not address this issue

b) Treatment for previously healthy people who develop severe influenza

From the point of view of the burden on the health service, the greatest pressure point in the 2009 H1N1 pandemic was demand for intensive care services for individuals with severe influenza and secondary complications. Since severe influenza and secondary complications are generally uncommon in seasonal influenza, NAI treatment trials did not have sufficient participants (ie were not sufficiently powered) to robustly evaluate the effect of treatment on complications and severe influenza, although a number of the trials did record information on these outcomes. It is therefore important to consider observational data from the 2009 H1N1 pandemic to improve our understanding of treating severe influenza.

Defining 'severe influenza'

The lack of clear definitions for severe influenza has implications for the interpretation of the evidence base, as it is difficult to come to conclusions until consistent definitions are applied. For example, different treatment approaches are likely to be required for patients with severe symptoms compared to those at high likelihood of death, both of which could be defined as 'severe influenza'. Current Public Health England guidance defines 'complicated influenza' (see Box 3).

Pneumonia

Pneumonia provides a useful example of the difficulties of assessing secondary outcomes. Some trials included patient-reported pneumonia as a secondary outcome, whereas others defined pneumonia when it was diagnosed by a clinician or a radiological test, such as an X-ray. Such differences can make it very difficult to compare findings. Experts at the workshop considered that although referring to patient-reported pneumonia as pneumonia is likely to create an unreliable finding, in the context of a double-blinded trial, this finding may nevertheless act as a useful indicator of participants' states of health.

Reduction in the incidence of pneumonia with NAI treatment was found to be significant in both the Cochrane and MUGAS meta-analyses: Cochrane – RR for pneumonia with oseltamivir 0.55 (95% CI 0.33 to 0.90); MUGAS –RR for pneumonia with oseltamivir for ITT population 0.34 (95% CI 0.18 to 0.64). However, this includes data based on patient-reported pneumonia. Cochrane repeated this test with data from trials where only clinically diagnosed pneumonia was considered and did not find a statistically significant treatment effect (RR for pneumonia 0.69 [95% CI 0.33 to 1.44]; n=1,136). In zanamivir trials, which included verified and unverified pneumonia, there was no significant treatment effect. In addition, no distinction was made in any of the trials between viral pneumonia caused by the influenza and secondary bacterial pneumonia. These factors make it difficult to draw firm conclusions from the evidence provided.

Hospitalised patients

Observational data from the 2009 H1N1 pandemic reported by the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) consortium showed that NAI treatment at any time was associated with a reduction in any cause mortality of *hospitalised* patients (adjOR for death 0.81 [95% CI 0.70 to 0.93])[61]. There are no randomised trials to inform decisions about treating previously healthy people who develop severe influenza.

[61] Muthuri *et al.* included data for patients admitted to hospital with laboratory confirmed or clinically diagnosed pandemic influenza A H1N1pdm09 virus. These findings are therefore not specific to 'previously healthy people'.

Current practice is to use NAIs when treating previously healthy people with 'complicated' influenza[62]. **The evidence from the PRIDE meta-analysis of observational studies during the 2009 H1N1 pandemic shows that deaths in hospitalised patients reduced when NAIs were used, and the steering group concludes that this supports the use of NAIs to treat influenza in patients who require hospitalisation.** However, the steering group notes that there were high levels of missing or unobtainable data in many of these analyses, and having RCT data in this setting would enhance the evidence base. This is considered further in the section on research priorities.

Box 3. Definitions in current UK guidelines

These definitions are from the 2015 Public Health England clinical guidelines[63], which apply to current circulating strains of influenza. They are very similar to definitions in other national and international guidelines, eg the 2014 United States Centers for Disease Control and Prevention (CDC) guidelines and the 2009 European Centre for Disease Prevention and Control (ECDC) guidelines. It is important to note that risk factors may vary between different seasonal and pandemic influenza strains (for example, older children were a high-risk group during the 2009 H1N1 pandemic), including factors in addition to those below.

Uncomplicated influenza ('not severe')

Influenza presenting with fever, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia) and sometimes gastrointestinal symptoms, but without any features of complicated influenza.

Complicated influenza ('severe')

Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

Risk factors for complicated influenza ('high risk')

- Neurological, hepatic, renal, pulmonary and chronic cardiac disease
- Diabetes mellitus
- Immunosuppression
- Age over 65 years
- Pregnancy (including up to two weeks postpartum)
- Age under six months
- Morbid obesity (body mass index [BMI] >=40)

[62] Public Health England. PHE Guidance on Use of Antiviral Agents for the Treatment and Prophylaxis of Influenza. London: Public Health England; 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/400392/PHE_guidance_antivirals_influenza_2014-15_5_1.pdf [accessed 29 July 2015].

[63] Public Health England. PHE Guidance on Use of Antiviral Agents for the Treatment and Prophylaxis of Influenza. London: Public Health England; 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/400392/PHE_guidance_antivirals_influenza_2014-15_5_1.pdf [accessed 29 July 2015].

c) Commencing treatment in severely ill individuals more than 48 hours after onset of symptoms

Analysis of retrospective observational data in the PRIDE study found that in hospitalised patients the benefit of NAI treatment was lost if treatment was commenced 48 hours after the onset of symptoms (comparison of late NAI treatment to no NAI treatment, adjOR for mortality 1.20 [95% CI 0.93 to 1.54]), although a benefit remained in patients admitted to an intensive care unit (ICU) (adjOR 0.65 [95% CI 0.46 to 0.93]).

Muthuri *et al*. suggest that the finding that no treatment was better than late treatment may be explained by the confounding related to how severely ill patients were when treatment was started[64]. It is likely that untreated patients had a milder form of disease and therefore demonstrated better outcomes, whereas patients treated later might have had delays in being admitted to hospital, diagnosed, or considered for NAI treatment.

The need for a better understanding of the window of effectiveness for NAI treatment is highlighted in the section on research priorities. However, the steering group also notes that while it is possible to define a window of effectiveness for NAIs in a particular setting, it is unlikely that this will be the same in all circumstances or for all individuals. For example, immunosuppressed people, the very old or the very young may show longer periods of viral replication, and therefore the window of effectiveness may be extended. In addition, different influenza strains may offset, reduce or extend the period of effectiveness depending on its replication period.

The steering group considers that the current evidence supports NAI treatment within 48 hours of the onset of symptoms. The evidence in support of treatment outside of 48 hours after the onset of symptoms is limited to cases of severely ill patients requiring ICU admission. Use outside of 48 hours after the onset of symptoms in other scenarios must therefore rely on clinical judgement, and the steering group notes that issues such as strain variation may affect the period of effectiveness. While the importance of initiating treatment as early as possible in those who do go on to develop severe disease is clear from these results, identifying these patients within 48 hours is not always possible.

d) Individuals with underlying health conditions that predispose them to complications of influenza (including pregnant women, older patients and those with underlying health problems)

Defining 'high risk'

Public Health England guidance defines 'risk factors for complicated influenza' (see Box 3, above). However, generally the term is not clearly defined and the additional risk to the groups identified is not adequately quantified. In addition, the groups of patients at high risk may vary between different strains. Existing definitions of high risk are based on the last pandemic, and prior to 2009 morbid obesity (where BMI is 40 or higher) would not have been considered a risk factor.

Most of the trials included in the meta-analyses are based on the treatment of patients in the community rather than of high-risk groups. There are few studies that focus specifically on high-risk groups and many trials actively exclude such patients. It is important that data and findings from

[64] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.

studies in an otherwise healthy population are not inappropriately applied to groups they are not relevant to. Overall, the evidence base for identifying and treating individuals at high risk of severe outcomes is weak.

The Cochrane meta-analysis did not perform sub-group analysis on specific high-risk groups. However, the MUGAS individual patient data meta-analysis defined a high-risk comorbidity subgroup of patients enrolled in a chronic illness trial or with chronic airways disease or aged older than 65 years, and the same group with the age group extended to patients aged older than 50 years. In these two high-risk groups no statistically significant benefit of oseltamivir was seen in the time to alleviation of all symptoms compared to a placebo (11.2 hours [95% CI, a reduction of 37.5 hours to an increase of 18.2 hours] and 18.1 hours [95% CI, a reduction of 39.7 hours to an increase of 5.1 hours] for those aged over 65 years and over 50 years respectively). In addition, no benefit in time to alleviation of all symptoms was seen in all participants aged older than 65 years compared to placebo (a reduction of time to alleviation of all symptoms of 17.4 hours [95% CI, a reduction of 49.8 hours to an increase of 15.6 hours]).

There is a paucity of evidence to guide decisions on NAI treatment of high-risk groups, and the steering group recognises that clinicians will need to balance the risks and benefits and may choose to offer this treatment to their high-risk patients.

Pregnant women

Pregnant women are considered to be a high-risk group by Public Health England. In pregnant women hospitalised in the 2009 H1N1 pandemic, the PRIDE study found that NAI treatment at any time substantially decreased mortality (adjOR for mortality 0.46 [95% CI 0.23 to 0.89]). This effect was more pronounced with treatment within 48 hours of symptom onset compared to none (adjOR for mortality 0.16 [95% CI 0.04 to 0.67]) and even compared to late treatment (adjOR 0.27 [95% CI 0.11 to 0.63]). However, the number of individuals included was relatively small (n=2,166 out of 9,513 female patients of reproductive age) compared to the total number of patients included in the study. **The steering group concludes that the current observational evidence supports the treatment with NAIs of pregnant women who are hospitalised with influenza**. RCT evidence would enhance the evidence base.

Children

Children under six months are the only group of children currently regarded as being at high risk of complications from seasonal influenza (Box 3). The PRIDE meta-analysis of observational data from pandemic influenza shows no benefit of oseltamivir in children in terms of mortality (<16 years; adjOR for mortality 0.82 with treatment at any time [95% CI 0.58 to 1.17]; p=0.28). The Cochrane review included only one relatively small trial of oseltamivir use in previously healthy children. This showed a benefit in the time to first alleviation of symptoms of 29.4 hours (95% CI 47.0 hours to 11.8 hours; n=669), although no benefit compared to a placebo was seen in children with asthma in another relatively small trial (n=660), and no difference in hospitalisations was observed. No statistically significant effect of zanamivir was seen in the same review (n = 723; time to first alleviation of symptoms reduced by 1.08 days; 95% CI a reduction of 2.32 days to an increase of 0.15 days). **The steering group considers that that there is insufficient evidence to guide decisions about the use of NAIs for treating influenza in previously healthy children. The steering group recognises that clinicians will need to balance the risks and benefits in each case and may choose to offer this treatment where the patient is a child.**

e) Prophylaxis of influenza

Prophylactic use of NAIs was seen to reduce the risk of influenza in individuals, based on RCT and observational data from seasonal and pandemic influenza[65] and RCT data from seasonal influenza[66] (oseltamivir: OR of confirmed influenza 0.11 [95% CI 0.06 to 0.20] and RR 0.45 [95% CI 0.30 to 0.67] respectively; zanamivir: OR 0.23 [95% CI 0.16 to 0.35] and RR 0.39 [95% CI 0.22 to 0.70] respectively). Both reviews also identified similar effects in household prophylaxis (see Table 3). **This evidence supports the use of NAIs for prophylaxis of influenza in individuals and households.** However, whether NAIs *should* be used in individual or household prophylaxis must take into account other factors, such as: the severity of the circulating strain; unwanted effects; immunisation prevalence and the match between the vaccine and circulating strain; the potential for NAI resistance in the circulating strain; and cost-effectiveness. In addition, the distribution of antivirals for prophylactic use creates challenges for public health and the health service. A trial in community care is needed to support an evidence-based approach for the prophylactic use of antivirals, and this is highlighted in the later section on future research.

The use of NAIs for prophylaxis in nursing homes is routine in the USA. Anecdotal evidence – including from the evidence-gathering workshop – suggests that this is a particularly contentious issue for some UK GPs. Often the exclusion criteria of trials prevent the patients that are resident in nursing homes from taking part, which means that the evidence on the use of prophylaxis in nursing homes is more limited than in other settings. In addition, nursing home residents are likely to have comorbidities that make treatment more difficult, eg chronic renal impairment.

There is a paucity of evidence from the recent studies to inform a single approach for prophylaxis in care homes. These decisions must therefore be made on a case-by-case basis using clinical judgement and be based on the severity of the outbreak. Further research is needed to inform decisions on whether or not to use NAIs in prophylaxis in care homes to understand the benefits and side-effects for individuals (unwanted effects may be higher in more frail, older people) and the wider implications for the health service.

[65] Okoli GN *et al*. Use of neuraminidase inhibitors for rapid containment of influenza: a systematic review and meta-analysis of individual and household transmission studies. PLoS ONE 2014;9(12). http://www.ncbi.nlm.nih.gov/pubmed/25490762 [accessed 29 July 2015].
[66] Jefferson T *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (review). The Cochrane Library 2014a;4. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/pdf [accessed 29 July 2015].

6. Pipeline of new drugs and resistance

In Europe only the neuraminidase inhibitors (NAIs) oseltamivir and zanamivir are licensed and recommended for the treatment of influenza at present[67]. Widespread resistance to the original class of influenza antivirals, the aminoadamantanes, among current seasonal and 2009 H1N1 pandemic strains of influenza means that they are not currently useful[68,69]. Recent reviews have concluded that there are significant unmet clinical needs, particularly for hospitalised, critically ill and immunocompromised patients. Combined with the emergence and spread of resistance to oseltamivir in seasonal H1N1 viruses in 2007 and 2008[70], it is important that the drug development pipeline delivers new agents for the treatment of influenza.

At the workshop Professor Frederick Hayden (Professor of Medicine and Pathology, University of Virginia) provided an overview of the diverse products in development and the prospects for future therapies, including new medicines and combination approaches expected to come to the market over the next decade[71].

- **New NAIs and drug delivery routes**
  Two novel NAIs, peramivir and laninamivir, have been approved in Japan. Peramivir was also approved in the USA in December 2014 for single-dose therapy of uncomplicated influenza, where it is the first NAI approved for intravenous (IV) administration. In addition, IV zanamivir is under development as another alternative to orally administered oseltamivir and orally inhaled zanamivir to improve drug delivery, in particular for seriously ill patients.

- **Small molecule therapies for novel viral targets**
  A number of drugs with alternative viral targets are in development. For example, favipiravir, currently in phase III trials[72], is thought to inhibit the viral RNA polymerase and appears to be active against influenza A, B and C as well as some other RNA viruses[73]. VX-787 is a new selective viral RNA polymerase inhibitor in phase II development that is active against influenza A viruses, including the 2009 pandemic and H5 influenza strains[74].

[67] Zambon M. Developments in the treatment of severe influenza: lessons from the pandemic of 2009 and new prospects for therapy. Cur Opin Infect Dis 2014;27(6):560–65.
[68] Ibid.
[69] Hayden F. Newer influenza antivirals, biotherapeutics and combinations. Influenza Other Respir Viruses 2012;7(suppl. 1):63–75.
[70] Takashita E *et al*. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2013–2014. Antiviral Res 2015;117:27–38.
[71] Academy of Medical Sciences and the Wellcome Trust. Supplementary material: use of neuraminidase inhibitors in influenza. London: Academy of Medical Sciences and the Wellcome Trust; 2015. http://www.acmedsci.ac.uk/snip/uploads/560d197898581.pdf [accessed 1 October 2015].
[72] MediVector. MediVector completes patient enrollment in two phase 3 studies of favipiravir for influenza. MediVector 2015 17 February. http://www.medivector.com/news/medivector-completes-patient-enrollment-in-two-phase-3-studies-of-favipiravir-for-influenza/ [accessed 29 July 2015].
[73] Hayden F. Newer influenza antivirals, biotherapeutics and combinations. Influenza Other Respir Viruses 2012;7(suppl. 1):63–75.
[74] Clark MP *et al*. Discovery of a novel, first-in-class, orally bioavailable azaindole inhibitor (VX-787) of influenza PB2. J Med Chem 2014;57(15):6668–78.

- **Monoclonal antibodies**
  Observations from the 1918 pandemic onwards have suggested that there is therapeutic value in the use of plasma from convalescent patients. Convalescent plasma is still being explored as an add-on therapy, but this has also led to the exploration of new monoclonal antibody therapies to treat influenza[75]. Portions of both the membrane proximal and the membrane distal regions of the haemagglutinin protein on the surface of the influenza virus that are very similar between strains are considered to be promising targets. Several monoclonal antibodies directed at these targets are currently in development, as are other monoclonal antibodies targeting different surface proteins, such as the extracellular domain of the influenza A M2 protein and the neuraminidase[76].

- **Host targets**
  Drugs targeted at the host pathways used by the virus during its replication provide a possible approach to treat influenza infection while minimising the risk of resistance emerging. For example, DAS181 (Fludase), an inhaled fusion protein containing a sialidase from a bacterium, is in phase II development for treating influenza. DAS181 removes sialic acid from the surface of cells in the host's airways, therefore preventing the virus from binding to and infecting the cells. Other possible targets include cell signalling pathways activated by influenza infection. However, limited progress has been made in this area at present and safety testing will be particularly crucial where host functions are targeted[77].

- **Combination therapies**
  Combination therapies for influenza treatment have been promoted for decades, since these have the potential to increase effectiveness and reduce the emergence of resistance. For example, together favipiravir and oseltamivir show a synergistic effect in preclinical models[78]. A triple combination of the aminoadamantane amantadine, ribavirin and oseltamivir showed synergistic activity against influenza A virus *in vitro* and in mouse models, even where the strain was amantadine or oseltamivir resistant[79]. Multiple clinical trials of therapeutic combinations, involving either outpatients or hospitalised patients with influenza, are currently in progress[80].

Influenza strains resistant to the commonly used NAIs, particularly oseltamivir, occur sporadically due to mutations in the viral neuraminidase. This is often, but not always, associated with NAI exposure[81]. Approximately 98 per cent of over 10,000 virus samples collected globally between May 2013 and May 2014 were sensitive to all four NAIs. However, around 2 per cent showed highly reduced inhibition against at least one of these drugs, and several substantial geographic clusters of oseltamivir resistance in the pandemic 2009 H1N1 virus have been identified[82].

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[75] Zambon M. Developments in the treatment of severe influenza: lessons from the pandemic of 2009 and new prospects for therapy. Cur Opin Infect Dis 2014;27(6):560–65.
[76] Hayden F. Newer influenza antivirals, biotherapeutics and combinations. Influenza Other Respir Viruses 2012;7(suppl. 1):63–75.
[77] Hayden F. Newer influenza antivirals, biotherapeutics and combinations. Influenza Other Respir Viruses 2012;7(suppl. 1):63–75.
[78] Zambon M. Developments in the treatment of severe influenza: lessons from the pandemic of 2009 and new prospects for therapy. Cur Opin Infect Dis 2014;27(6):560–65.
[79] Hayden F. Newer influenza antivirals, biotherapeutics and combinations. Influenza Other Respir Viruses 2012;7(suppl. 1):63–75.
[80] Academy of Medical Sciences and the Wellcome Trust. Supplementary material: use of neuraminidase inhibitors in influenza. London: Academy of Medical Sciences and the Wellcome Trust; 2015. http://www.acmedsci.ac.uk/snip/uploads/560d197898581.pdf [accessed 1 October 2015].
[81] Meijer A *et al*. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2012–2013. Antiviral Res 2014;110:31–41.
[82] Takashita E *et al*. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2013–2014. Antiviral Res 2015;117:27–38.

Resistance to oseltamivir has often been associated with reduced transmission of the virus[83]. However, in the winter of 2007-08 a highly transmissible seasonal H1N1 oseltamivir-resistant influenza virus emerged, with around 14 per cent of the circulating strains found to be resistant, compared to less than 1 per cent in previous years[84]. During the subsequent months it spread globally to completely replace the susceptible strain.

The steering group notes that resistance was not a significant clinical issue in the 2009 H1N1 pandemic, except in some highly immunocompromised or critically ill patients[85]. However, present problems with bacterial resistance to antimicrobials illustrate the potential outcome of unrestricted prescribing. There are products in the development pipeline of pharmaceutical companies that could provide alternatives to NAIs, either alone or in combination, and it is important that these products are progressed.

[83] Lackenby A *et al*. Continued emergence and changing epidemiology of oseltamivir-resistant influenza A(H1N1)2009 virus, United Kingdom, winter 2010/11. Eurosurveillance 2011;16(5). http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19784 [accessed 29 July 2015]
[84] Lackenby A *et al*. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Eurosurveillance 2008;13(5).http:/www.eurosurveillance.org/viewarticle.aspx?articleid=8026%20 [accessed 29 July 2015].
[85] http://www.who.int/influenza/patient_care/antivirals/2011_09_23_weekly_web_update_oseltamivir_resistance.pdf [accessed 6 August 2015].

7. Future research

Throughout the report areas where further research would strengthen the evidence base have been highlighted. The 2009 H1N1 pandemic was a missed opportunity to conduct research, randomised controlled trials (RCTs) in particular, that could have addressed uncertainties in the evidence base and informed practice. It is vital that the UK does not miss such opportunities in the future. In addition to informing practice in itself, the steering group heard at the workshop that further research is important for raising the quality of available evidence so as to build trust in the evidence base among medical practitioners and patients. In the absence of a robust evidence base the steering group considers it unethical not to perform research to inform practice, and has identified specific priorities for research, which are discussed below. In all cases it is important to identify the questions to be answered and then the most appropriate method of doing so. Also addressed is the need to be prepared to act quickly in the event of a new pandemic or severe seasonal outbreak.

Future RCTs

As outlined above, the current RCT data cannot be used to address some of the key unanswered questions; for example, such trials are often underpowered for important endpoints, such as some of the rarer side-effects, and the current data are not based on a pandemic. The existing RCT data have already been extensively exploited, and there is very limited value to be obtained from further secondary analysis. New RCTs are therefore a key way to address outstanding questions about the risks and benefits of neuraminidase inhibitors (NAIs), since they would provide high-quality, unbiased evidence on efficacy to inform policy decisions.

Previous trials of NAIs have been traditional placebo-controlled RCTs. Consideration should be given to novel approaches for clinical trials, such as pragmatic or adaptive designs that are also being explored in other disease areas, eg assessments of cancer therapies and the treatment of Ebola[86]. These trials can allow flexibility to add new potential treatments as they become available or drop interventions as soon as they are shown to be ineffective, and can compare different interventions without requiring a control arm. Pragmatic trials such as these therefore provide more relevant (so-called 'real world') data and can be particularly useful for providing important evidence on the cost-effectiveness of an intervention in conditions that approximate usual clinical practice.

Given the weaknesses in the current evidence base, the steering group considers that it is essential to conduct new high-quality and adequately powered RCTs to address key uncertainties.

[86] Cooper BS *et al*. Evaluating clinical trial designs for investigational treatments of Ebola virus disease. PLoS Med 2015;12(4). http://www.ncbi.nlm.nih.gov/pubmed/25874579 [accessed 29 July 2015].

Prospective observational studies

Prospective observational studies – where data are collected to address specific questions about interventions, rather than relying on retrospective analysis of routinely collected data – will play an important role in building the evidence base, particularly where it is not possible to perform RCTs. In addition to the key areas highlighted below, prospective studies would be useful for improving understanding of which individuals are at the highest risk of poor outcomes and how they should be treated.

Key questions to be addressed by new RCTs and prospective observational studies

a) RCTs of NAI use in hospitalised patients and in high-risk groups.
The observational data on hospitalised patients and high-risk groups can be used to estimate the number of participants needed to ensure an adequately powered trial. Calculations suggest that around 800 participants might be needed, depending on the endpoints selected[87]. At the evidence-gathering workshop the challenges of RCTs in hospitalised patients, particularly those in intensive care units (ICUs), were debated in some detail. Of particular concern was the ethical issue of having a placebo arm containing seriously ill patients. However, to mitigate these difficulties consideration should be given to novel designs for clinical trials, including the adaptive trial designs discussed above, that may be more efficient and reduce the chances of any one individual being allocated to a treatment approach that is ineffective.

The steering group is sympathetic to the challenges that traditional, placebo-controlled RCTs would raise for clinicians and patients in a pandemic scenario. However, **subject to ethical and regulatory approval, the steering group concludes that conducting RCTs of NAI use in hospitalised patients and in high-risk groups is a high priority.**

b) Large pragmatic trial of NAI treatment in primary care.
The workshop and review of studies revealed that there is considerable uncertainty around the use of NAIs for influenza-like illness treatment in primary care, particularly in understanding the benefits and costs. New evidence of cost-effectiveness from pragmatic trials is needed to support decisions about whether and how NAIs should be used in practice in seasonal and pandemic influenza, and if so, which subgroups might benefit most.

c) Studies of household prophylaxis to consider the cost-effectiveness and wider implications of prophylaxis, such as distribution and resistance.
The limited evidence on the cost-effectiveness of NAIs for household prophylaxis needs to be addressed in seasonal and pandemic influenza. This research could contribute to a better understanding of the severity threshold at which it becomes cost-effective to use NAIs in prophylaxis.

[87] At the workshop, Professor Carl Heneghan noted that 864 participants would be required to have an 80 per cent chance of detecting a decrease in mortality from 10 per cent in the control group to 5 per cent in the experimental group, at a 5 per cent significance level. Fewer participants are needed assuming a 70 per cent reduction in mortality, as observed in Hsu *et al*. 2012 (http://www.ncbi.nlm.nih.gov/pubmed/22371849 [accessed 29 July 2015]): 382 patients would be required to have an 80 per cent chance of detecting a decrease in mortality from 10 per cent in the control group to 3 per cent in the experimental group, at a 5 per cent significance level.

d) Studies of prophylaxis in care homes.
The evidence base on the prophylactic use of NAIs in care homes is weak for pandemic and seasonal influenza. Further research is needed to improve understanding of the benefits and side-effects for individuals and the wider implications for the health service. Cluster randomised trials are feasible but would need to be large scale.

e) Pharmacokinetics-pharmacodynamics (PKPD) studies to improve understanding of the effective dose for NAIs and their use in combinations.
Studies are needed to delineate the PKPD relationship of NAIs in influenza, in the use of combinations, and in populations potentially at risk or in whom dose adjustment may be needed (for example obese patients, pregnant women, those with renal failure, the immunocompromised, infants and the elderly). Studies on PKPD at the sites of infection in the lungs are also needed.

f) More accurately defining the time window for effective NAI treatment.
Current evidence on the time window for NAI use is based on observational studies. While this suggests that treatment after 48 hours is not valuable except in ICU patients, it is highly unlikely that in practice this is a straightforward cut-off point. Further research is needed to more accurately define the time window for effective NAI treatment.

Rapid tests for influenza infection

There was extensive discussion at the workshop about the value of rapid tests for influenza infection, particularly as the current evidence base suggests that NAIs are not active against other respiratory viral infections. However, some attendees noted that influenza outbreaks were readily recognised by the volume of activity in GP surgeries, especially in the appropriate season. At present, polymerase chain reaction (PCR) based assays are the gold standard for testing for influenza infection; they are usually performed only in secondary care and in laboratories rather than at the bedside. In order for tests to be useful for guiding the use of NAIs in practice, they need to be cost-effective (NAIs are relatively cheap), be reliable and provide rapid results (particularly given the 48-hour window). Even if appropriate tests were available, attendees at the workshop highlighted the logistical challenges of administering these tests in GPs' surgeries or at pharmacies.

Health services and social science research

It is important to understand the impacts of an influenza epidemic and its different treatment strategies on the health service and public health system. For example, at the workshop concerns were raised that some NAI distribution strategies in the previous pandemic may have brought together individuals who were not infected with infectious individuals, counter to public health advice. Understanding the impacts on the health service is also particularly important where implementation of new guidelines or technologies, such as the introduction of near-patient diagnostics, could be expected to lead to changes in demand for particular services. Health services research has an important role to play in learning from current strategies and ensuring that effective planning is in place for the future. The steering group envisages that health services research would be important to inform effective practice in the following areas:

- distribution of NAIs, including for prophylaxis
- behaviour of healthcare professionals and understanding how guidance is implemented
- implementation of public health measures
- providing additional resources when necessary, such as medical staff, wards, ventilators and extracorporeal membrane oxygenation.

Pre-agreed protocols (‘sleeping protocols’)

For both RCTs and prospective observational studies the UK must be in a position to act immediately in a new epidemic or pandemic, with pre-agreed protocols, relevant approvals, funding and infrastructure in place beforehand. The aim should be to ensure that data gathering and RCTs can be put into action within days. This approach should allow findings to be available rapidly to inform practice in a current outbreak, as well as in the future.

The steering group strongly endorses the development and use of pre-agreed protocols and approvals and considers that these should apply to many of the research priorities that are discussed in this report. The steering group advises that these protocols must be able to be initiated immediately at the onset of a new epidemic or pandemic, which requires clearly defined ‘ownership’ and responsibility for activation of such protocols. Scenario planning and exercises in preparation for such a pandemic should include a thorough assessment of the ability to initiate studies within such a time frame that considers staff, administration, funding, ethics approval and data collection.

8. Concluding remarks

This section sets out the steering group's concluding remarks, but does not repeat its specific conclusions, which are set out in the introductory summary.

Most seasonal influenza is self-limiting and, taking into account the risk-benefit balance, the evidence does not support the use of neuraminidase inhibitors (NAIs) for all patients who are not severely ill. Although the 2009 H1N1 influenza pandemic was relatively mild, an influenza pandemic remains a very real threat to the social and economic wellbeing of the UK. Conclusions based on seasonal influenza cannot be simply extrapolated to an epidemic or pandemic situation where there might be a greater risk of worse outcomes for the individual or the population as a whole. In such a situation widespread use of NAIs may become justified as the risk-benefit balance changes. The severity of an outbreak of influenza and the risk of poor outcomes is unlikely to be known at the start of an epidemic or pandemic, or even at the start of the influenza season. The time to gain that information and make evidence-based decisions is limited, and rapid sharing of information about a new strain of influenza is critical to informing rational decision making.

Decisions about the use and stockpiling of antivirals are based on a range of considerations, including economic, public health, political and ethical factors as well as the scientific evidence that is considered here. Although the scientific evidence base is not as strong as it could be, there is clear evidence that NAIs provide some benefit in the treatment of influenza. This report sets out ways in which the scientific evidence base should be strengthened. However, in the meantime the UK government will have to make difficult policy decisions based on incomplete evidence and in the face of competing priorities. The more severe the pandemic (in terms of strain virulence and severity of symptoms), the greater the likelihood of treatment benefiting the population. Given the difficulty of predicting the impact of an influenza outbreak at an early stage, some governments, including the UK's, have decided that it is prudent to be prepared, in advance, to provide NAIs for treatment and prophylaxis to a large proportion of the population in a severe pandemic.

The health-economic consequences of widespread NAI use are not well understood. The US and EU patents for zanamivir have already ended and the patent for oseltamivir ends in 2016[88,89]. The cost of these drugs may fall as a result of coming off patent, increasing the cost-effectiveness of their use. However, this is not guaranteed, due to difficulties in their manufacture and uncertainty in the market that might make these drugs unattractive to generic drug companies. However, it is important to note that an increase in the cost-effectiveness of these drugs would not affect their underlying efficacy and effectiveness, or the need for studies to understand these better.

[88] Patents for zanamivir: https://www.ipo.gov.uk/p-ipsum/Case/PublicationNumber/EP0734382 [accessed 7 August 2015] and https://www.ipo.gov.uk/p-ipsum/Case/PublicationNumber/EP0526543 [accessed 7 August 2015].
[89] Roche Tamiflu factsheet 2006. http://www.roche.com/tamiflu_factsheet.pdf [accessed 6 August 2015]. See page 2.

The lack of evidence available to the steering group in preparing its commentary has underlined the fact that an important opportunity was missed to undertake randomised controlled trials (RCTs) and prospective observational studies in the last pandemic. There is uncertainty among some clinicians about the relationship between the evidence base and existing advice, not least because of the public debate about the latest analyses. Additional research to address the evidence gaps – and particularly RCTs of NAI use in hospitalised patients and in high-risk groups – is a priority, and the steering group outlines other areas where additional research would be valuable.

There are particular difficulties inherent to the design and conduct of clinical trials of treatment or prophylaxis of influenza, and to the interpretation and application of their results in clinical and public health practice. These include the features of the virus that make it such a potentially dangerous pathogen, particularly genetic changes among strains and new strains emerging from other species. This limits the certainty with which trial results can be extrapolated between strains, and makes it particularly important that new studies can be initiated quickly. Preparedness planning for an influenza epidemic or pandemic should include a thorough assessment of the ability to activate pre-agreed protocols (so-called sleeping protocols) for research programmes immediately at the onset of a new epidemic or pandemic. A further difficulty is that the clinical settings for these trials are likely to be challenging – for example involving large numbers of subjects in primary care or severely ill patients in intensive care – and these difficulties will be exacerbated by the additional organisational and capacity pressures on the health service of seeking to manage an epidemic or a pandemic. It is important that the difficulties of conducting such trials are appreciated when assessing the implications and limitations of existing research, but strategies should nevertheless be found to ensure that these challenges do not prevent requisite new research from going ahead.

Annex 1: Biographies and declared interests of steering group members

Professor Sir Patrick Sissons FMedSci (Chair)
Sir Patrick was formerly Clinical Vice President of the Academy of Medical Sciences (until December 2014). From 1998 he was Professor of Medicine at the University of Cambridge, and then Regius Professor of Physic and Head of the university's School of Clinical Medicine from 2005 until retiring in 2012. His personal research on the biology and pathogenesis of human cytomegalovirus infection is supported by a Medical Research Council programme grant, which now continues under his colleagues in the School of Clinical Medicine. He was previously a non-executive director of Cambridge University Hospitals NHS Foundation Trust, and is currently a non-executive director of Cambridgeshire and Peterborough NHS Foundation Trust and a board member of the National Medical Research Council of Singapore.

Professor Jeffrey Almond FMedSci
Professor Almond is Visiting Professor to the Medical Sciences Division at the University of Oxford. He was a member of the Council of the Medical Research Council from 2008 to 2014, and was previously Head of Discovery Research and External R&D at Sanofi Pasteur, which he joined in 1999. He was also previously Professor of Microbiology at the University of Reading. He is currently Director of Greenbank Bio Ltd (a biotechnology consultancy), a shareholder in Sanofi, and consultant to and acting Executive Chairman of VirionHealth Ltd.

Professor Deborah Ashby OBE FMedSci
Professor Ashby is Chair in Medical Statistics and Clinical Trials and Co-Director of the Imperial Clinical Trials Unit at Imperial College London. Previously she was Chair in Medical Statistics at Barts and the London School of Medicine and Dentistry, Queen Mary University of London, and held academic appointments at the University of Liverpool. She has served as a member of the UK Commission on Human Medicines and regularly advises the European Medicines Agency. She chairs the Research Methods Programme for the National Institute for Health Research (NIHR). She has previously served on the Council of the Royal Statistical Society. She has held many grants as a coapplicant and as a department head – from NIHR, the Medical Research Council, Cancer Research UK, the British Heart Foundation and the Wellcome Trust – mainly for clinical trials, and has also received Innovative Medicines Initiative funding for methodology projects. A member of Professor Ashby's family also works for the UK Department of Health as the lead analyst for nonelective care performance (with some other responsibilities, including planning for influenza).

Professor Chris Butler

Professor Butler is Professor of Primary Care at the University of Oxford and a general medical practitioner in South Wales. He is Clinical Director of the University of Oxford Primary Care Clinical Trials Unit. He is the Workpackage leader of the EU FP7-funded “Antivirals for influenza-like illness? An RCT of clinical and cost effectiveness in primary care” (ALIC4E) study, which is part of the Platform for European preparedness against (re-)emerging epidemics (PREPARE) consortium. He is on the MRC Efficacy and Mechanisms Evaluation Board of the Medical Research Council. He is the Chief investigator of the “Point of care testing to target antibiotics for chronic obstructive pulmonary disease exacerbations” (PACE) study which has been supported in the form of a non-restrictive educational grant of the loan of C-Reactive Protein assay machines and associated support from the international diagnostics company Alere. He has also received fees personally from Alere for presenting and participating in a workshop on point of care testing using C-Reactive protein for common infections in primary care.

Dr Jeremy Farrar OBE FMedSci

Dr Farrar has been Director of the Wellcome Trust since 2013. He was previously Director of the Oxford University Clinical Research Unit in Vietnam. He has served on World Health Organization advisory committees, and is currently on the board of directors of Genome Research Ltd and a member of the council of the Foundation for Science and Technology.

Sir John Skehel FRS FMedSci

Sir John is Emeritus Scientist at the Francis Crick Institute, Mill Hill, London, and Biological Secretary of the Royal Society. He was Director of the WHO Collaborating Centre for Reference and Research on Influenza from 1975 to 1994 and Director of the National Institute for Medical Research, Mill Hill, from 1987 to 2006.

Annex 2: Workshop agenda and attendees

Agenda

Arrival	
09.00	**Registration and coffee**
Morning session	
09.30	**Welcome** Professor Sir Patrick Sissons FMedSci, University of Cambridge
09.40	**Clinical importance of seasonal and pandemic influenza** Professor John Watson, Deputy Chief Medical Officer, UK Department of Health
09.50 11.10	**Evidence review** Chair: Professor Sir Patrick Sissons FMedSci, University of Cambridge Presentation of recent studies: • Professor Carl Heneghan, University of Oxford • Professor Jonathan Nguyen-Van-Tam, University of Nottingham • Mrs Joanna Dobson, London School of Hygiene and Tropical Medicine Discussion session
12.45	**Lunch**
Afternoon session	
13.45	**Emerging resistance and pipeline of new treatments** Chair: Professor Jeffrey Almond FMedSci, Visiting Professor, Medical Sciences Division, University of Oxford Speaker: Professor Fred Hayden, University of Virginia Discussion session
14.30	**Discussion of research priorities, tractable questions and methodological improvements** Chair: Sir John Skehel FRS FMedSci, Francis Crick Institute, Mill Hill, London
16.15	**Wrap-up and thanks** Professor Sir Patrick Sissons FMedSci, University of Cambridge
16.30	**Close**

Attendees

	Name	Position and institution
Steering group	Professor Sir Patrick Sissons FMedSci (Chair)	Emeritus Regius Professor of Physic, University of Cambridge
	Professor Jeffrey Almond FMedSci	Visiting Professor, Medical Sciences Division, University of Oxford
	Professor Deborah Ashby OBE FMedSci	Chair in Medical Statistics and Clinical Trials, Imperial College London
	Professor Chris Butler	Professor of Primary Care, University of Oxford
	Sir John Skehel FRS FMedSci	Emeritus Scientist, Francis Crick Institute
Participants	Dr Stephen Brett	Consultant in Intensive Care Medicine, Imperial College Healthcare NHS Trust
	Professor Mike Catchpole	Chief Scientist, European Centre for Disease Prevention and Control
	Dr Barry Clinch	Principal Clinical Scientist, Roche
	Dr Deb Cohen	Centre for Evidence-Based Medicine, University of Oxford
	Mrs Joanna Dobson	Lecturer of Medical Statistics, London School of Hygiene and Tropical Medicine
	Sir Gordon Duff FRSE FMedSci	Former Chairman, Medicines and Healthcare Products Regulatory Agency
	Dr Nick Francis	Reader, Institute of Primary Care and Public Health, University of Cardiff
	Professor Fred Hayden	Professor of Medicine and Pathology, University of Virginia
	Dr Andrew Hayward	Professor of Infectious Disease Epidemiology and Inclusion Health Research, University College London
	Professor Carl Heneghan	Director, Centre for Evidence-Based Medicine, University of Oxford
	Professor Peter Horby	Group Leader, Epidemic Disease Research Group Oxford, University of Oxford
	Professor Menno de Jong	Professor of Clinical Virology, University of Amsterdam
	Dr John Middleton	Vice President for Health Policy, Faculty of Public Health
	Professor Arnold Monto	Professor of Epidemiology, University of Michigan

	Professor Jonathan Nguyen-Van-Tam	Professor of Health Protection, University of Nottingham
	Professor Karl Nicholson	Emeritus Professor of Infectious Diseases, University of Leicester
	Professor Peter Openshaw FMedSci	Professor of Experimental Medicine, Imperial College London
	Professor Tim Peters FMedSci	Professor of Primary Care Health Services Research, University of Bristol
	Dr Philip Price	Senior Portfolio Adviser, Wellcome Trust
	Dr Nikki Shindo	Medical Officer, World Health Organization
	Dr Helen Steel	Vice President, Infectious Diseases Therapeutic Area, GlaxoSmithKline
	Professor Garry Taylor	Professor of Molecular Biophysics, University of St Andrews
	Professor Alain Townsend FRS	Professor of Molecular Immunology, University of Oxford
	Professor Thomas Walley CBE FMedSci	Director, National Institute for Health Research Health Technology Assessment (HTA) and Efficacy and Mechanism Evaluation (EME) Programmes; Professor of Clinical Pharmacology, University of Liverpool
	Professor John Watson	Deputy Chief Medical Officer, UK Department of Health
	Dr David Wright	Deputy Manager, Statistics and Pharmacokinetics Unit, Medicines and Healthcare Products Regulatory Agency
	Professor Lucy Yardley	Professor of Health Psychology, University of Southampton
	Professor Maria Zambon FMedSci	Director of Reference Microbiology Services, Public Health England
Secretariat	Mr David Bennett*	Policy Officer, Academy of Medical Sciences
	Dr Richard Parker	Policy Intern, Academy of Medical Sciences
	Dr Rachel Quinn*	Director of Medical Science Policy, Academy of Medical Sciences
	Dr Beth Thompson*	Policy Adviser, Wellcome Trust

* Denotes the secretariat for this project

Annex 3: Current policies and guidance with regard to terms of reference

	United States Centers for Disease Control and Prevention, 2014[90]	Public Health England, 2015[91]	World Health Organization, 2009[92]	European Centre for Disease Prevention and Control, 2009[93]	Japan Pandemic Influenza Experts Advisory Committee, 2007[94]	Communicable Diseases Network Australia, 2011[95]
Treatment for previously healthy people with influenza that is not (currently) severe ('treat all' approach)	Consider within 48 hours of onset of symptoms	No – unless the physician feels there is a serious risk of developing serious complications from influenza	No	Yes – within 48 hours	Yes – for pandemic influenza "It is extremely important to contain infection… Therefore, preventive administration will be performed… to prevent the spread of infection."[96] Not for seasonal influenza	Consider – use clinical judgement

[90] United States Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. Centers for Disease Control and Prevention; 2014. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm [accessed 6 August 2015].
[91] Public Health England. PHE guidance on use of antiviral agents for the treatment and prophylaxis of influenza. London: Public Health England; 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/400392/PHE_guidance_antivirals_influenza_2014-15_5_1.pdf [accessed 6 August 2015].
[92] World Health Organisation. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. World Health Organisation; 2009. http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf [accessed 6 August 2015].
[93] European Centre for Disease Prevention and Control. ECDC Interim Guidance: Public Health Use of Influenza Antivirals During Influenza Pandemics. Stockholm: European Centre for Disease Prevention and Contro; 2009. http://ecdc.europa.eu/en/publications/Publications/0907_GUI_Public_Health_use_of_Influenza_Antivirals_during_Influenza_Pandemic.pdf [accessed 6 August 2015].
[94] Pandemic Influenza Experts Advisory Committee. Guideline for Antiviral Drugs. Japan: Pandemic Influenza Experts Advisory Committee; 2007. http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/pdf/09-e10.pdf [accessed 6 August 2015].
[95] Communicable Diseases Network Australia. Influenza Infection: CDNA National Guidelines for Public Health Units. Communicable Diseases Network Australia; 2011. http://www.health.gov.au/internet/main/publishing.nsf/Content/3D622AEAE44DDEB2CA257BF0001ED884/$File/Influenza-SoNG-july11.pdf [accessed August 2015].
[96] Pandemic Influenza Experts Advisory Committee. Guideline for Antiviral Drugs. Japan: Pandemic Influenza Experts Advisory Committee; 2007. http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/pdf/09-e10.pdf [accessed 6 August 2015]. See page 183.

	United States Centers for Disease Control and Prevention, 2014[90]	Public Health England, 2015[91]	World Health Organization, 2009[92]	European Centre for Disease Prevention and Control, 2009[93]	Japan Pandemic Influenza Experts Advisory Committee, 2007[94]	Communicable Diseases Network Australia, 2011[95]
Treatment for previously healthy people who develop severe influenza	Yes – preferably within 48 hours of the onset of symptoms	Yes – for patients with 'complicated' influenza (influenza requiring hospital admission/symptoms and signs of lower respiratory tract infection). Treatment should be started as early as possible, but should always be given, no matter how long after the onset of the illness	Yes	Not discussed	Yes	Consider – use clinical judgement
Commencing treatment in severely ill individuals more than 48 hours after onset of symptoms	Yes	Yes – treatment should be started as early as possible, but should always be given, no matter how long after the onset of the illness	Yes	Yes	No	No

	United States Centers for Disease Control and Prevention, 2014[90]	Public Health England, 2015[91]	World Health Organization, 2009[92]	European Centre for Disease Prevention and Control, 2009[93]	Japan Pandemic Influenza Experts Advisory Committee, 2007[94]	Communicable Diseases Network Australia, 2011[95]
Treatment for individuals with underlying health conditions that predispose them to complications of influenza (including pregnant women) who develop influenza	Yes – any time, not just within 48 hours of the onset of symptoms	Yes – treatment should be started as early as possible, but should always be given, no matter how long after the onset of the illness. For pregnant women, treatment should be started as early as possible, preferably within 48 hours of the onset of symptoms. After this time, clinical judgement should be exercised	Yes	Not discussed	Yes	Consider – use clinical judgement
Prophylaxis	No	Only discusses post-exposure prophylaxis. Individuals who were previously healthy (excluding pregnant women) should not be given prophylaxis. Prophylaxis is only advised for at-risk groups	Not discussed	Yes	Yes – if limited geographical spread	Only in high-risk patients

Annex 4: Definitions of statistical terms used in the report

Intention to treat (ITT) analyses are used to assess clinical effectiveness. In an ITT analysis all participants randomly assigned to one of the treatments are analysed together, regardless of whether or not they dropped out, fully adhered to a treatment or switched treatment. In the case of trials discussed in this report, all patients given neuraminidase inhibitor (NAI) treatment were included in ITT analyses, regardless of whether or not they had confirmed influenza. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice.

Intention to treat infected (ITTI) analyses only consider participants in which there has been a confirmation of the infection. In influenza reports an ITTI analysis would mean that influenza had been confirmed with laboratory testing.

An **odds ratio (OR)** is a measure of the relative likelihood of an outcome, such as mortality. An odds ratio is calculated by dividing the probability of mortality in the intervention group by the same probability in the control group. If the outcomes of the participants are the same in both groups, then the odds ratio will be 1. An odds ratio greater than 1 suggests that the control is better than the intervention, while an odds ratio of less than 1 suggests that the intervention is better than the control. For example, if there was a 0.75 chance of mortality for patients in the placebo group and a 0.25 chance of mortality in the treatment group, the odds ratio would be 0.33. An **adjusted odds ratio (adjOR)** is a ratio where researchers have attempted to control for the confounding effects of other variables. For example, Muthuri *et al*.[97] were concerned about the confounding effect of the 'propensity' of antiviral treatment, where antiviral drugs may have been prioritised towards the sickest patients, which could have affected the odds ratio of mortality. Researchers therefore may opt to control for confounding variables, like treatment propensity, using statistical techniques such as logistic regression.

Relative risk or a **risk ratio (RR)** is the ratio of the risk of illness among those exposed to certain conditions compared with the risk for those exposed to different conditions. For example, researchers could compare the risk of people who smoke getting lung cancer with the risk for people who do not smoke. If the risk for each of these two groups was calculated and it was found that people who smoke had an RR of 2.5, then this would mean people who smoke are 2.5 times more likely to get lung cancer than non-smokers. If both groups face the same level of risk, the RR would be 1.

Number needed to treat to benefit (NNTB) reflects the average number of patients who would need to be treated to get a positive outcome in one patient. For example, where NNTB=5, five patients would need to be treated to ensure that one of them gets better. The closer NNTB is to 1, the better the treatment, as NNTB=1 means that a positive outcome is expected for every patient treated.

Number needed to treat to harm (NNTH) reflects the average number of patients that would need to be exposed to a risk to see a negative outcome in one patient. For example, if NNTH=1,000, then 1,000 patients would need to be exposed to a risk for one of them to have an adverse outcome. The higher the number, the lower the occurrence of adverse effects, with the expectation therefore being that more patients could be given a treatment before one person is expected to have an adverse outcome.

[97] Muthuri SG *et al*. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014;2(5):395–404.

Annex 5: Strengths and limitations of randomised controlled trials and observational studies[98]

Study type	Strengths	Weaknesses
Randomised controlled trials (RCTs)	• Good internal validity (extent to which the data can be used to address the specific question under consideration) • Provide precise measures of efficacy of new therapies under ideal conditions • Measurement of effect size is less prone to bias • Allow exploratory measures of secondary endpoints • Can evaluate prognostic and predictive properties of new biomarkers	• Limited external validity (extent to which findings can be generalised to other settings, such as different patient groups) • Provide evidence of efficacy, but not of effectiveness (ie true benefit to patients in routine practice) • Applicability to clinical practice can be limited: o patients and practitioners are different from those in routine practice o the elderly and patients with comorbidity are underrepresented o often powered to detect a clinically modest effect size that may not apply to a wider group of patients o may use a primary endpoint that is not a valid measure of patient benefit o have limited ability to detect rare and chronic toxicities, especially those that occur in patients with comorbidity or that emerge after completion of the trial
Observational studies	• Good external validity • Provide insight into delivery of care in routine practice to all patients, including the elderly and those with comorbidity • Provide information to guide future knowledge translation • Can provide evidence of effectiveness of new therapies in the general population • Can address questions that have not, and will not, be evaluated in an RCT, for example where ethical issues would prevent randomisation	• Limited internal validity: may be difficult to separate effects of a new treatment from other factors • Population-level databases often do not include detail regarding comorbidity, performance status and specific treatment plan • Identification of comparative benefit in these studies is prone to multiple biases, including confounding by indication for a given treatment and/or concurrent changes in practice and/or disease biology

[98] This table is based on: Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer 2014;110(3):551–5.

The Academy of Medical Sciences

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Wellcome Trust
Gibbs Building
215 Euston Road
London NW1 2BE, UK
T +44 (0)20 7611 8888
F +44 (0)20 7611 8545
E contact@wellcome.ac.uk
wellcome.ac.uk