FAQs relating to the *Lancet Respiratory Medicine* publication: *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*

1. What is this study about?

The aim of the PRIDE study (**P**ost-pandemic **R**eview of anti-**I**nfluenza **D**rug **E**ffectiveness) was to investigate the association between the use of neuraminidase inhibitor (NAI) antivirals (see Related Question l) and outcomes of public health importance in pandemic influenza A(H1N1)pdm09 patients using an individual participant data (IPD) meta-analysis (see Related Question b). Public health outcomes of interest in hospitalised patients include mortality, admission to critical care facilities, length of stay in hospital and influenza-related pneumonia. This study will also investigate the association between NAI antivirals prescribed in the community and hospitalisation due to pandemic A(H1N1)pdm09 influenza.

The recently published paper in *The Lancet Respiratory Medicine* journal, reports the findings from the investigation of the association between NAI antivirals and mortality in pandemic A(H1N1)pdm09 patients. These analyses have been conducted in a standardised pooled dataset comprising 29,234 individual hospitalised A(H1N1)pdm09 patients from across the world.

2. Who is part of the PRIDE research consortium?

The PRIDE research consortium comprises 155 researchers representing 81 study centres from 38 countries who contributed their data for inclusion in the individual participant data meta-analysis. The coordination of the consortium, standardisation, pooling of data and analysis is being carried out by a project team based at the University of Nottingham under the strategic leadership of Professor Jonathan Nguyen Van-Tam. A complete list of the PRIDE consortium members and their affiliations can be found in the Supplementary information Appendix 1.

3. Who is funding this research?

The salaries for the two Research Associates working as part of the University of Nottingham project team were funded via an unrestricted educational grant from F. Hoffman- La Roche, Switzerland (the manufacturers of oseltamivir (Tamiflu®)), for research in the area of pandemic influenza. Dr Puja Myles is the principal investigator named on this grant. No payments were made to any of the PRIDE study consortium members for data collection. The terms of the grant can be viewed on the PRIDE Study website.

4. You have a clear conflict of interest as this work has been funded by F. Hoffman- La Roche, the pharmaceutical company that manufactures and markets Tamiflu®. Why should I believe your findings?

The Funder has had no role in protocol design, no opportunity to comment on it, and no opportunity to see it other than via the PROSPERO website; no access to any data (and no rights to future access); no role in analysis or interpretation; no opportunity to preview results/findings before entry into the public domain; no opportunity to contribute to, preview or comment on manuscripts and presentations arising from this work. The research contract between the University of Nottingham and the Funder is freely available for inspection (commercial details redacted) on the PRIDE Study website.

5. Are the data included in your study truly representative of the global reality?

Our pooled dataset includes data from 38 countries and 81 research groups. The initial identification of potential data contributors was identified on the basis of a systematic search strategy which was last updated on the 19th of April 2012 as described in the publication by Muthuri et al. (2012). This was itself a formal systematic review and meta-analysis, searching 11 databases and conforming to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Like the present study, it was registered on PROSPERO (CRD 42011001273). This study by Muthuri et al. (2012) formed the starting point for our recruitment of data contributors; however we continued on from there using a 'snowballing strategy' via the PRIDE study website, our existing network of collaborators (many of whom are global

influenza experts) and invitations extended to colleagues via announcements at influenza specific conferences and opportunistically. We believe we have used an exhaustive search strategy to identify datasets relating to the pandemic without just being reliant on already published literature. In spite of these efforts we agree that we cannot guarantee that we have captured all relevant data but we are confident that we have included the major surveillance datasets from across the globe.

6. Was it appropriate to combine data from so many different settings?

This is a valid concern as there may be differences in baseline mortality experience, hospital admission and treatment protocols across various study settings. This was one of the reason we adopted a multilevel modelling (see Related Question g) approach in our analyses, which essentially takes into account such differences across various study centres. This is a well-recognised methodological approach to deal with these sorts of differences.

7. Did you include any data from trials conducted by pharmaceutical companies in your study?

We did not include any data from trials conducted by pharmaceutical companies in our study. No pharmaceutical company supplied any of our data. In fact, we did not include any experimental trial data in our study and nor did we expect to find any such studies given that it would have been unethical in an influenza pandemic to withhold NAI antiviral treatment from patients.

8. We have noticed that your study does not include data from a study by XYZ et al. Why have you not included all relevant data in your study?

We used a systematic approach based on published papers, conference abstracts, calls for participation via influenza-specific conferences and the PRIDE study website and recommendations from influenza experts, to identify datasets that could be used to investigate the association between NAI antivirals and public health outcomes during the 2009 A(H1N1)pdm09 influenza pandemic. As a result of the systematic approach, we identified and contacted 401 potential data contributors. Centres fulfilling the minimum dataset requirement were eligible for inclusion. We received replies from 128 (32%) of 401 centres contacted; of these 77 (60%) confirmed willingness to participate and the remainder declined (no data: 36 (28%); agreed initially but later withdrew: 3 (2%) (lack of capacity for data extraction, IRB restrictions preventing sharing of individual participant data and failure to obtain government approval for data sharing); agreement in principle, but unable to share data within project timescales: 12 (9%)). In spite of this exhaustive approach it is possible that we may have missed some datasets. As part of our commitment to transparency of research and public health, if we are notified of such datasets we will incorporate these into our existing pooled dataset and repeat our analyses to ensure that our published findings are still valid. These results will be posted on this website and a research letter updating our findings will be submitted to the *Lancet Respiratory Medicine* journal.

9. What was the proportion of deaths from pandemic influenza in your study sample? What was the number and proportion of patients on Tamiflu or similar antivirals in your study, who died?

10% of the A(H1N1)pdm09 influenza patients in our dataset died. 66% of deaths occurred in A(H1N1)pdm09 patients receiving NAI treatment at any stage of illness. Among A(H1N1)pdm09 patients receiving early NAI treatment within 48 hours of illness onset, we observed 20% mortality. These proportions should be interpreted with caution as they do not take into account illness severity at time of receiving treatment. One of the limitations of non-experimental data on treatment is that it is susceptible to confounding by indication (see Related Question d) i.e. sicker patients are more likely to receive NAI treatment and untreated patients are likely to have had milder disease.

10. What are the key study findings?

Our results show that neuraminidase inhibitor (NAI) treatment was associated with reduced mortality in adult patients admitted to hospital with A(H1N1)pdm09 virus infection. NAI treatment at any stage of illness compared to no NAI treatment was associated with an approximately 20% reduction in likelihood of death (25% in adults only as reported in other press releases). Early NAI treatment (within 48 hours of illness onset) was associated with an approximately 50% reduction in likelihood of death when compared either to no NAI treatment or later NAI treatment. These findings were statistically significant or in other words, highly unlikely to be observed purely by chance.

11. Do your findings primarily relate to Tamiflu?

Our study considered neuraminidase inhibitor (NAI) antivirals (see Related Question l) as a group. This includes the drugs oseltamivir (Tamiflu®), zanamivir (Relenza®) and peramivir (Rapiacta®). Amongst those who received NAI antivirals in our data, 92% received oral oseltamivir, 2% received intravenous or inhaled zanamivir and less than 1% received intravenous peramivir. These are not mutually exclusive categories as 1% of patients received more than one NAI antiviral during the course of their illness. For 7% of our patients, we could not identify the specific NAI drug used, but it is most likely to have been oral oseltamivir.

12. Did your study consider Tamiflu® (oseltasmivir) and Relenza® (zanamivir) separately?

Our study investigated NAI antivirals as a class though 92% of the patients received oseltamivir. Our dataset did not have enough people taking other NAI antivirals (zanamivir or peramivir) for us to be able to run separate statistical analyses for these drugs.

13. Could your study findings that patients receiving NAI antivirals were less likely to die, be explained by other treatments that they may have been provided?

Disentangling the effects of NAI antivirals from other treatments such as antibiotics and corticosteroids is important which is why we took these other treatments into account in our analyses. Our adjusted analyses results showed that even after taking into account other treatments in hospital, NAI antivirals were associated with a statistically significant reduction in mortality.

14. What does your study tell us about the use of antivirals in pregnant women?

We observed statistically significant reductions in mortality of about 54% associated with NAI treatment at any stage of illness among pregnant women. Early NAI treatment within 48 hours of illness onset was associated with a statistically significant reduction in the likelihood of death by about 80% when compared to no NAI treatment.

15. What does your study tell us about the use of antivirals in children?

Our study did not find a statistically significant reduction in mortality associated with NAI use in children (under the age of 16 years). This finding held when we investigated the association in children less than 5 years and in those under one year.

16. Based on your study findings should doctors stop prescribing Tamiflu® and similar antivirals in children?

Whilst we were consistently unable to demonstrate any significant reduction in mortality in children associated with NAI use there may be a variety of explanations for our findings: fewer deaths in paediatric patients (thus limited statistical power), higher influenza A(H1N1)pdm09 viral load in children leading to reduced drug effectiveness, sub-optimal dosing in very young children, secondary bacterial infections (e.g. MRSA), confounding by indication (see Related Question d), or a combination of these. Therefore, we are hesitant to recommend firmly against the use of NAIs in children because several of the results, while being statistically non-significant, could suggest a reduction in mortality. We think our findings need wider debate post-publication before conclusions should be drawn.

17. Your recommendation to provide antivirals as early as possible following illness onset, preferably within 48 hours, is unlikely to be feasible for most people.

This is a valid concern for patients, doctors and policy makers, especially since influenza symptoms are non-specific and it may be hard to tell them apart from similar illnesses caused by non-influenza viruses. This is why we investigated both Early NAI treatment provided within 48 hours of illness onset, and NAI treatment given at any stage of illness. In both cases we observed significant reductions in mortality as compared to no NAI treatment, though the mortality reduction benefits were greater with early NAI treatment. This suggests that on balance, treatment with NAI antivirals may have significant mortality reduction benefits at the population level even when it is not possible to provide treatment within the 48 hour window following illness onset. The accompanying Editorial article by Dr Alicia Fry makes it clear that: "As expected, early treatment seems to be optimal, and treatment shouldn't be delayed by even 1 day to wait for diagnostic test results; however, if the patient presents for care more than 2 days after illness onset, treatment might still have some benefit, especially if they are severely ill."

18. I am a doctor who frequently sees possible influenza cases but they rarely consult me within 48 hours of illness onset. Should I bother prescribing antivirals at all in such cases?

Our findings show that significant mortality reduction benefits can be achieved at the population level even when NAI treatment is provided after 48 hours following illness onset. On this basis it is advisable not to withhold NAI treatment solely because you are not sure whether the patient has presented to you within 48 hours of illness onset. The Editorial comment from Dr. Alicia Fry at CDC states: "As expected, early treatment seems to be optimal, and treatment shouldn't be delayed by even 1 day to wait for diagnostic test results; however, if the patient presents for care more than 2 days after illness onset, treatment might still have some benefit, especially if they are severely ill."

19. Based on your study findings, how late after illness onset can antivirals like Tamiflu be prescribed and expected to make a difference?

Our findings suggest that there is a detriment in the survival benefit associated with each day's delay in NAI treatment beyond 2 days from illness onset. We were unable to establish the length of delay following treatment onset at which point treatment with NAI would offer no mortality reduction benefits over no NAI treatment. However, in critically ill adult patients we observed a significant mortality reduction of about 35% even with NAI treatment administered more than 2 days after illness onset, when compared to no NAI treatment.

20. Most people with influenza do not die as a result of it. Does this mean that antiviral drugs like Tamiflu® are only of benefit in a severe pandemic or in patients who are at increased risk of influenza-related adverse outcomes?

When compared to previous influenza pandemics, the 2009 A(H1N1)pdm09 influenza pandemic is considered mild in terms of the morbidity and mortality experience. In spite of this, in our sample we observed about 10% mortality across all age groups and demonstrated significant mortality reduction benefits at the population level. Our study also found that mortality was not restricted to patients usually categorised at high-risk of influenza-related adverse outcomes and 47% of the patients who died did not have any of the comorbidities typically associated with influenza-related adverse outcomes. Based on our results we advocate that treatment may be of benefit in patients who are ill enough to be hospitalised with influenza. But because not all patients present to hospital within 48 hours of symptom onset, treatment in the community of patients who are appreciably unwell (and at risk of hospitalisation) with influenza-like illness may also be appropriate.

21. More people appear to have died in the antiviral treated group in your study and yet we observe a protective effect with antiviral treatment. How is this possible?

Yes, more people in the antiviral treated group died compared to those who were not treated. However, this can be explained if people in the treated group had a higher baseline risk of dying as compared to the people in the untreated group. We therefore have a problem of non-equivalent comparison groups.

Ideally, we would conduct a randomised controlled trial (experimental study) where equivalent patients are randomly assigned treatment or a sugar pill (placebo). This way if we observe any differences in patient outcome, we can be more confident that these could be attributed to treatment status alone. In a pandemic situation, it would have been unethical to randomly deny antiviral treatment to patients. This meant we only had the option of studying actual treatment practice and the patient outcomes resulting from this during the 2009 influenza pandemic. In order to overcome the issue of comparing non-equivalent patient groups, we use statistical methods to 'adjust' for any patient differences to allow us to disentangle treatment effects from outcomes arising due to fundamental differences among patients. This is why the adjusted results should be considered and not the crude (unadjusted) results. The crude results are only presented in the interest of transparent scientific reporting.

22. A recent criticism in an article published in the Medical Observer includes the following quote from Dr Mark Jones, a biostatistician from the University of Queensland, ""This analysis does not take into account time-dependent bias, which we have found is large in observational studies of influenza". On this basis the article claims that your study is flawed. How would you respond to such a critique of your methodology?

We have acknowledged the point about time-dependent treatment effects (see Related Question h) in our paper. Time-dependent treatment effects can impact findings such that treatment can appear to be favourable as compared to no treatment because of a bias termed 'immortal time bias' which is observed because patients who die early do not get an opportunity to receive treatment. Moreover, in Dr Jones' words, "In addition patients who are extremely sick may not be given the opportunity to receive treatment." In fact based on the reported clinical experience of treating patients during the 2009 pandemic we believe the opposite may be more likely – that for patients in the Intensive Care Unit (ICU) especially, the sickest patients, the most critically ill, are the most likely to be treated with antivirals, not the reverse. This is precisely why, for the subset of our population, where dates of illness onset and antiviral administration were available, we used a time-dependent Cox regression shared frailty model. Even after using this approach we found an approximately 50% reduction in mortality associated with NAI antiviral treatment.

23. Do your findings only relate to the 2009 influenza pandemic or can they be applied to future pandemics?

While our data relate to the pandemic A(H1N1)pdm09 influenza virus, based on the mechanism of action of NAI antivirals, it is reasonable to consider these findings applicable to other influenza viruses such as influenza A H3N2 or influenza B, and to other pandemics.

24. Did your study find any adverse events related to the use of Tamiflu® or similar antivirals?

Our study did not investigate adverse events related to the use of NAI antivirals.

25. Your findings appear to be in conflict with previously published research on Tamiflu®. How do you explain this?

Our findings are consistent with previous evidence on the effectiveness of NAI antivirals in reducing adverse outcomes related to the pandemic influenza A(H1N1)pdm09 virus. Previously we published a systematic review of published studies in the Journal of Infectious Diseases that found a statistically significant 65% reduction in mortality associated with early NAI treatment provided within 48 hours of illness onset as compared to no NAI treatment. We did not however find a statistically significant association between NAI treatment at any stage of illness and a reduction of mortality as compared to no

NAI use. The primary limitations of this previous review was the variety of methods used across these studies which is why the PRIDE study was conceptualised as a means of overcoming these methodological problems by bringing together datasets from across the world for analysis in a standardised way.

26. What are the implications of these findings for public health policy?

Our findings strongly suggest that early treatment with NAI antivirals in adults admitted to hospital with suspected or proven influenza infection can yield a clinically meaningful reduction in mortality.

27. Based on your study findings, would you recommend replenishing of antiviral stockpiles by governments?

Our study findings endorse the policy decisions to stockpile and use NAI antivirals in hospitalised patients during the 2009 A(H1N1)pdm09 influenza pandemic. Given the inherent delays in developing and deploying a pandemic virus strain specific vaccine during a pandemic and the absence of other anti-influenza treatment options, neuraminidase inhibitors are clearly an important component of pandemic response. We offer these data for governments to consider, in the round, as they contemplate any independent decisions they make about replenishment of antiviral stockpiles as part of their pandemic preparedness strategy. We believe it is better to make these decisions, supported by data, but recognise that prior to 2009 many governments had to make decisions on less than adequate data.

28. Based on your study findings, is there any evidence to support the stockpiling of Tamiflu® in preference to other similar antivirals?

Our study investigated NAI antivirals as a class though 92% of the patients received oseltamivir. Our dataset did not have enough people taking other NAI antivirals (zanamivir or peramivir) for us to be able to run separate statistical analyses for these drugs. Therefore, our study findings are most generalisable to oseltamivir. However, there are other considerations when deciding on which of the NAI antivirals to stockpile including efficacy of prophylaxis, ease of administration, safety profile, antiviral resistance, storage and economics.

29. Given the recent controversy over Tamiflu and your funding source, would you be willing to share your data with other scientists so that your findings can be confirmed?

Ideally, in the spirit of transparency, we would have a publicly accessible pooled dataset so that other researchers can validate our analyses. In reality though, we are subject to data sharing agreements with our data contributors and may not be given permission by individual research groups within the PRIDE consortium or their local ethics boards to share this data even in a pooled format. We will revisit this discussion with all our data contributors once we have completed all our planned analyses outlined in the PRIDE study protocol. We have however endeavoured to be transparent in the reporting of our methods and can make available our Stata code used for the analyses and our Stata log files to researchers who would like to scrutinise our work on application to Professor Jonathan Nguyen Van-Tam (jvt@nottingham.ac.uk). We are also available for clarifications regarding our published findings.

RELATED QUESTIONS

a) What is a systematic review?

In clinical medicine and public health, it is important to base decisions on sound scientific evidence. Systematic reviews use a structured approach to identify, critically appraise and synthesise all available evidence on a well-defined research question. Systematic reviews can include published and unpublished evidence to provide an unbiased perspective on the evidence. Often, systematic reviews are accompanied by meta-analyses which provide a pooled measure of effect for association under study.

b) How is an individual participant data meta-analysis different from a meta-analysis?
Conventionally, a meta-analysis of published studies is performed by pooling study level effect estimates to derive an overall pooled effect estimate. An Individual Participant Data (IPD) meta-analysis differs from conventional meta-analyses in that the pooling is performed at the individual participant level, i.e. participant data are obtained from the original investigators for each included study, standardised and then incorporated into a single pooled dataset for analysis. IPD analyses allow for standardised variable definitions, statistical methods and adjustment for a standardised list of confounders.

c) What do you mean by 'publication bias'?
Studies that show positive or statistically significant findings are more likely to be published by journals when compared to studies showing no association or studies with non-significant findings. This tendency of journals to publish studies with positive findings results in publication bias. Consequently, any pooled estimates resulting from a synthesis of such studies would also show a positive effect which is likely to be an inaccurate representation of the true association. The extent of publication bias in a meta-analysis can be tested and, to a certain extent, corrected for as well.

d) What is meant by 'confounding by indication'?
Confounding by indication is seen in observational (i.e. non-experimental) studies where study participants are not randomly allocated to receive treatment and the decision to treat a patient is most often made on the basis of the clinical condition of the patient. If the clinical condition of the patient is likely to influence the outcome under study, the association between the treatment and the outcome could be confounded (muddled) by the factor triggering the treatment decision (treatment indication).

For example, a clinician may decide not to treat severely ill patients in the advanced stages of disease, because of a lack of perceived effectiveness of the drug in such patients, and may instead choose to prescribe the drug to mild or moderately ill patients reasoning that treatment may be more beneficial to such patients. In such an instance, although it may seem as if those patients who received the drug were less likely to die, this association is confounded by the fact that treatment was only administered to low-risk patients (patients with mild/moderate disease) in the first place. An alternative scenario is also possible where only the most severe patients are treated resulting in an apparent increase of complications/death in treated patients as compared to non-treated patients. So confounding by indication could work to falsely strengthen OR falsely weaken the findings about a drug's effectiveness.

e) What is a propensity score?
Propensity scores are used in non-randomised studies to adjust for confounding by indication by generating a probability value for each patient receiving a particular treatment given the presence of factors that may have influenced the clinician's decision to prescribe treatment to each patient. For instance, patient-related factors such as age, sex, severity of illness, underlying comorbidities may all influence a clinician's decision to prescribe a treatment. Propensity scores take into account these differences between patient groups and facilitate comparison between two non-randomised groups.

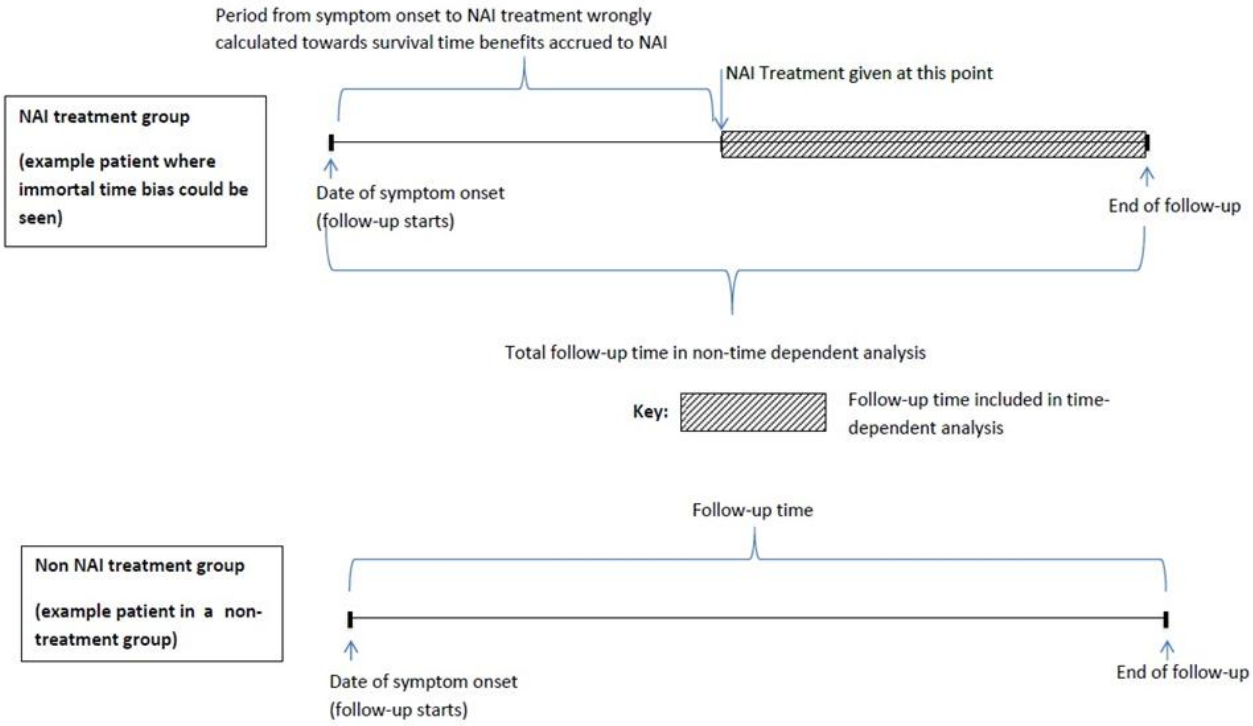
f) What do you mean by 'clustering' of effects?
We used data from 78 study centres across the globe. It is conceivable that there may be differences at the study level such as differences in the way healthcare is provided, accessibility to treatment, payment for healthcare or prescriptions etc. that could introduce further differences (heterogeneity) in our study. This is why it is standard statistical practice to account for these study level differences by performing 'clustered' analyses also known as multilevel modelling.

g) What do you mean by multilevel modelling?
When data are collected from more than one setting, certain study characteristics cause the data from a particular setting to 'cluster' together. For instance, in a global dataset, participants from a study centre in

Canada tend to be more like each other than, say, participants from a centre in Spain. In such a scenario it would be incorrect to simply pool such data together and ignore the differences between study centres. A multilevel modelling approach enables us to adjust for this 'clustering' and make data from multiple centres more comparable.

h) What are time-dependent treatment effects and how can you control for these in your statistical analysis?

Time-dependent treatment effects can impact findings such that treatment can appear to be favourable as compared to no treatment because of a bias termed 'immortal time bias' which is observed because patients who die early do not get an opportunity to receive treatment. Therefore, when comparing treated and untreated patients, it is important to compare survival time only after treatment is initiated in the treated group (time dependent analysis). An alternative analysis that ignores such time-dependent effects would compare survival in both treated and untreated groups from the point of illness onset. This is further explained diagrammatically.



i) How is influenza treated?

Uncomplicated cases of influenza do not usually need antiviral treatment. The decision to treat with antiviral drugs is usually made taking into account the patient's clinical condition and the presence of underlying risk conditions (for example, as recommended in UK NICE guidance). It is important to note, however, that since neuraminidase inhibitor drugs work by inhibiting viral replication, they are more effective when administered during the early stages of infection. Where there is evidence of secondary bacterial infections, such as pneumonia, antibiotics may also be prescribed.

j) Is seasonal influenza different from pandemic influenza?

An influenza pandemic is caused by the emergence of a novel strain of influenza virus capable of spreading globally and against which majority of the general population lack immunity. Seasonal influenza refers to the spike in influenza activity observed annually during winter months in temperate parts of the world.

Many people tend to have some level of immunity to seasonal influenza from exposure to the virus in previous years. However pandemic viruses become seasonal after the pandemic. For example the A(H1N1)pdm09 virus that caused the 2009 pandemic is new circulating as a winter seasonal virus.

k) Do we need to test for influenza before we give someone influenza specific antivirals?

Neuraminidase inhibitors work only against influenza viruses and would therefore be ineffective against other infections. While it may be ideal to first perform a lab confirmation of influenza before initiating NAI antivirals, treatment may be initiated following a clinical diagnosis of flu, especially considering the beneficial effects of NAIs when administered during the early stages of influenza. In the accompanying Editorial, Dr Alicia Fry from CDC states: "As expected, early treatment seems to be optimal, and treatment shouldn't be delayed by even 1 day to wait for diagnostic test results; however, if the patient presents for care more than 2 days after illness onset, treatment might still have some benefit, especially if they are severely ill."

l) How do Tamiflu® and other similar antivirals work?

Tamiflu belongs to a class of influenza virus-specific antiviral drugs called neuraminidase inhibitors (NAI). These drugs act by binding to neuraminidase proteins on the surface of influenza viruses and inhibiting viral replication. NAI drugs only inhibit replication of the virus and therefore it important for these drugs to be administered in the early stages of the infection when there is less virus in the body.

m) Why can we not just vaccinate people against influenza rather than stockpiling antivirals?

Flu viruses change continuously and vaccines tend to be strain specific, i.e. a vaccine developed for a particular strain of influenza may not confer complete immunity to a newer strain. In a pandemic situation, the virus is very novel, by definition. Currently available seasonal vaccines will not work and there is typically a delay of 5-6 months in developing and distributing (in large quantities) a pandemic influenza virus specific vaccine. In that time the new virus can spread a long way and cause many thousands of deaths. Antiviral drugs are not strain specific but instead act on the structure of the influenza virus. If they are available they can be used at once to treat patients.

n) Are there any documented adverse effects associated with NAI antivirals?

Nausea is fairly commonly experienced soon after starting treatment with oseltamivir, but tends to subside thereafter. Other less common adverse effects include: vomiting, stuffy nose, headache, diarrhoea and behavioural abnormalities have also been observed with NAI antiviral drugs. For each drug please consult the Summary of Product Characteristics for a full listing of adverse events, available at: www.medicines.org.uk