Neuraminidase inhibitors for influenza: a review and public health perspective in the aftermath of the 2009 pandemic

Charles R. Beck,a,* Rachel Sokal,b,* Nachiappan Arunachalam,c Richard Puleston,a Anna Cichowska,d Anthony Kessel,d Maria Zambon,e Jonathan S. Nguyen-Van-Tam,a,c on behalf of the UK Antiviral Effectiveness Review Group**1

aHealth Protection and Influenza Research Group, Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, Nottingham, UK. bPublic Health Directorate, NHS Derbyshire County, Matlock, UK. cHealth Protection Agency East Midlands, Institute of Population Health, Nottingham, UK. dPublic Health Strategy Division, Health Protection Agency, London, UK. eMicrobiology Reference Services, Health Protection Agency, London, UK.

Correspondence: Rachel Sokal, Public Health Directorate, NHS Derbyshire County, Chatsworth Hall, Chesterfield Road, Matlock, DE4 3FW, UK. E-mail: rachel.sokal@nhs.net

*These authors contributed equally to this work.

**UK Antiviral Effectiveness Review Group: Gabriel Agboado, Sakthidharan Karunanithi, Rob Howard, Rachel Cloke, Samia Latif, Joanne Enstone.

Objectives The objectives of this study were to: (1) reflect on key stages in the discovery, development and pre-pandemic use of neuraminidase inhibitors (NAIs), (2) summarise the evidence of NAI effectiveness for treatment and prophylaxis of seasonal influenza prior to the 2009 pandemic, and (3) summarise the evidence base generated during the 2009 pandemic period.

Design A rapid systematic review of evidence published to June 2010 was conducted where existing high-quality systematic reviews formed a baseline and were supplemented with data from other reviews, randomised controlled trials (RCTs) and observational studies.

Main Outcome Measures Severity and duration of symptoms; rates of severe illness, complications and death following treatment for influenza or influenza-like illness; rates of influenza and influenza-like illness following long-term prophylaxis or post-exposure prophylaxis of household contacts.

Results Prior to the 2009 pandemic, evidence from RCTs conducted in seasonal influenza epidemics indicated that NAIs used to treat laboratory-confirmed influenza in healthy adults reduced the duration of illness by one day. NAIs provide high levels of protective efficacy in adults when given long-term or in household-based post-exposure prophylaxis for seasonal influenza. Several 2009 pandemic period observational studies suggest that early treatment may reduce rates of hospitalisation and in-hospital mortality, but data from that period do not substantially increase the evidence base on prophylaxis, although they confirm effectiveness.

Conclusions NAIs should be deployed during a future pandemic for either post-exposure prophylaxis or treatment depending on national policy considerations and logistics. The existing evidence base on effectiveness against severe outcomes requires supplementation.

Keywords Clinical effectiveness, neuraminidase inhibitors, pandemic influenza, seasonal influenza.

Introduction Neuraminidase inhibitors (NAIs) are widely regarded as the only class of influenza-specific antiviral drugs that are suitable for use during an influenza pandemic. Two drugs, oseltamivir (Tamiflu®; F. Hoffmann-La Roche) and zanamivir (Relenza®; GlaxoSmithKline plc.), were first licensed in 1999 and at present remain the only two licensed products available in the United Kingdom (UK), although newer compounds from the same drug class (e.g. peramivir; BioCryst Pharmaceuticals Inc., and laninamivir; Daiichi Sankyo Co. Ltd.) have very recently been licensed in parts of the Far East including Japan and South Korea. The initial licensure of both zanamivir and oseltamivir was based on proof of a reduction in symptom duration and/or severity in treated healthy patients; but despite the evidence of individual clini-
between 1 May 2009 and 31 December 2009,12 and data from the USA show that 97.5% of prescriptions for NAIs during the pandemic were for oseltamivir.15

This review charts the discovery and development of NAIs and summarises the evidence base that was available before their deployment en masse during the 2009 pandemic, which with hindsight, has been recognised to be of similar lethality to seasonal influenza, albeit in younger age groups. We present the results of a rapid systematic review conducted for the UK government in the aftermath of the 2009 pandemic on the effectiveness of NAIs for the treatment and prophylaxis of influenza. The methodology is described in full elsewhere;14 existing high-quality systematic reviews formed a baseline for the evidence review which was supplemented by data from literature reviews, RCTs and observational studies.

Drug development, safety and indications for use

The importance of neuraminidase (NA) in the viral replication pathway has stimulated research into suitable therapeutic drugs targeting the enzyme. Studies published in the 1970s described the potential mechanism of action for N-acetylneuraminic acid and 2-deoxy-2,3-dehydro-N-trifluoroacetylneuraminic acid as transition-state analogues of sialic acid. In the early 1980s, the crystal structure of NA was determined and the catalytic site characterised,15–18 leading to the rational design and synthesis of zanamivir in 1989.19 Because clinical trials of zanamivir showed poor bioavailability and rapid excretion after oral administration, oseltamivir was developed as an alternative orally administered therapy.20 Clinical evidence from RCTs has previously demonstrated a similar efficacy of zanamivir and oseltamivir in both prophylaxis and treatment, contrary to their differing formulations and mode of administration.21–23

Adverse events associated with zanamivir are rare but clinically significant (including bronchospasm and allergic phenomena).7 Adverse events associated with oseltamivir include gastrointestinal symptoms, bronchitis and cough, dizziness and fatigue and neurological symptoms (e.g. headache, insomnia and vertigo); some of these may of course be attributable to influenza infection itself. Skin rashes, allergic reactions and rarely hepatobiliary disorders have also been reported. The incidence of side effects is low except for nausea and vomiting associated with oseltamivir treatment and prophylaxis. This effect tends to be transient, is reduced by dosing with food, is most marked in children and is supported by recent data from the 2009 pandemic period.24

There is a substantial literature regarding a potential association between oseltamivir and neuropsychiatric adverse events, especially in children and adolescents. It is unclear to what extent these data reflect neuropsychiatric manifestations of influenza infection or a genuine but rare effect of treatment; as such, a causal link has not yet been established.7 The data in favour of an association with treatment are somewhat skewed towards usage in Japan, which has a historically high usage of NAIs. Influenza-related encephalopathy is also regularly reported in the literature relating to Japan, and the suicide rate is high in that country.
Zanamivir is licensed for use in patients aged over 5 years, whilst oseltamivir may be used in patients of all ages. Below 1 year of age, the use of oseltamivir should be based on an individual risk-benefit assessment by the attending physician. Although licensing does not restrict the use of either NAI to otherwise healthy individuals, the product characteristics highlight the lack of evidence of clinical effectiveness and safety in at-risk patient groups including those with unstable chronic illness, those immunocompromised and those with chronic respiratory or cardiac disease.

Evidence of effectiveness for treatment and prophylaxis of seasonal influenza prior to the 2009 pandemic

Do neuraminidase inhibitors reduce the duration or severity of symptoms?

A number of randomised, double-blind, placebo-controlled trials exist which address this question. Most offer analyses based on intention-to-treat (ITT; treatment for clinically diagnosed influenza-like illness) as well as intention-to-treat influenza (ITTI; laboratory-confirmed influenza). In Tables 1 and 2, we summarise the results from a series of meta-analyses conducted by Burch et al. to describe the clinical effectiveness of zanamivir and oseltamivir in terms of alleviation of influenza symptoms and return to normal activity. These should be read in conjunction with this section because pooled effect sizes and p values (where available) are reported therein.

For healthy adults, there is strong, statistically significant, RCT evidence that zanamivir or oseltamivir given within 48 hours of symptom onset for ILI (ITT) reduces the time to symptom alleviation by approximately 0.5 days. For laboratory-confirmed influenza, the magnitude of benefit rises to approximately 1 day. When comparing the time taken to return to normal or baseline activity, no significant effect is seen for zanamivir based on ITT or ITTI, but a significant effect is observed for oseltamivir of 32- and 63-hour benefit, respectively.

In adults with at-risk conditions, there is strong, statistically significant, RCT evidence that zanamivir given within 48 hours of symptom onset for ILI (ITT) reduces the time to symptom alleviation by approximately 1 day. For laboratory-confirmed influenza (ITTI), the magnitude of benefit rises to approximately 1-7 days. Similar analyses for oseltamivir did not reach statistical significance. In terms of the time taken to return to normal or baseline activity, no significant effect is seen for zanamivir based on ITT or ITTI endpoints, but for oseltamivir, a significant effect is observed of 59- and 71-hour benefit, respectively. The pooled analysis of ITTI patients treated with zanamivir showed statistically significant heterogeneity across studies included.

For the treatment of patients aged 65 years and over, no significant effects are seen for zanamivir for ITT or ITTI endpoints. However, there is strong, statistically significant, RCT evidence that oseltamivir treatment within 48 hours of symptom onset for ILI (ITT) reduces the time taken to return to normal or baseline activity by 98-hour benefit; for ITTI endpoints, this benefit paradoxically decreases to 74 hours.

In children, there is strong, statistically significant, RCT evidence that both zanamivir and oseltamivir, given within 48 hours of symptom onset for ILI (ITT), reduce the time to symptom alleviation by almost 1 day. For laboratory-confirmed influenza (ITTI), the magnitude of benefit is similar. In terms of the time taken to return to normal or baseline activity, no significant effect is seen for zanamivir based on ITT or ITTI, but for oseltamivir, a significant effect of approximately 30-hour benefit is observed for both activity-related groups.

The additional pooled analyses and observational studies we identified showed similar findings to Burch et al. However, Lalezari et al. and Singh et al. showed larger effect sizes of treatment, resulting in statistically significant reductions in time to alleviation of symptoms in ITTI at-risk adults treated with zanamivir (median difference 2.5 days, \( P = 0.015 \)) and ITTI healthy adults treated with oseltamivir (median difference 23.9 hours, \( P < 0.0001 \), respectively. Singh et al. also reported a significant reduction in time to perform normal daily activities following treatment with oseltamivir (median difference 46.4 hours, \( P < 0.0001 \)).

Do neuraminidase inhibitors reduce the likelihood of developing severe illness, complications (including antibiotic requirement and hospitalisation) or death?

Overall, fewer RCT data are available to address this question. Burch et al. reported a pooled analysis of two RCTs which showed a statistically significant reduction in use of antibiotics following treatment with oseltamivir within 48 hours of symptom onset for ITT healthy adult patients (odds ratio 0.37, 95% CI 0.29–0.48, \( P < 0.001 \)). This analysis was, however, strongly influenced by a trial undertaken by Deng et al. where a high rate of antibiotic use was observed in both arms. The effect was maintained for ITTI patients in a separate meta-analysis (odds ratio 0.52, 95% CI 0.27–1.00, \( P = 0.05 \)). However, other assessed endpoints including bronchitis, pneumonia and rate of hospitalisation showed no significant evidence of effectiveness. Seasonal influenza complications in healthy adults are extremely rare; therefore, it is highly likely that the identified studies were underpowered to detect these events.

In at-risk adults, Burch et al. reported a statistically significant reduction in the incidence of bronchitis in patients with clinically diagnosed influenza treated with zanamivir (odds ratio 0.41, 95% CI 0.24–0.70, \( P = 0.0009 \)). Evidence
of a statistically significant effect following treatment with oseltamivir in at-risk adults was restricted to a 40% reduction in antibiotic use, but only for confirmed influenza cases (odds ratio 0.57, 95% CI 0.33–0.98, \( P = 0.04 \))."
evidence shows approximately a 50% reduction in antibiotic use (odds ratio 0.50, 95% CI 0.30–0.84, P-value not stated) and otitis media (odds ratio 0.52, 95% CI 0.33–0.82, P-value not stated) in children with confirmed influenza (ITT).9,31

Many additional observational studies from pre-2009 have examined the likelihood of complications in patients treated with NAIs, which support the results from RCT data regarding reductions in antibiotic requirement.32,33 However, several observational studies also suggest that the incidence of respiratory complications, pneumonia, major cardiac events and hospitalisation is reduced by oseltamivir treatment in healthy and at-risk adults.32–43 Observational study data (mainly related to smaller hospital studies, patients aged 65 years and over or immune-compromised populations) also suggest that mortality is reduced by oseltamivir treatment in at-risk adults.43–46 In children, there are observational data that support reductions in antibiotic requirements and the incidence of otitis media, pneumonia, and hospitalisation in oseltamivir-treated individuals.34,36–39,47 The observational data for zanamivir are less expansive but support similar conclusions for children. Overall, the observational data supporting a reduction in pneumonia are those that are least consistent with RCT evidence, and the data supporting a reduction in subsequent antibiotic use are the most persuasive.

Do neuraminidase inhibitors used for long-term prophylaxis reduce the risk of seasonal influenza disease?

In healthy adults, the protective efficacy of zanamivir in reducing symptomatic laboratory-confirmed influenza (SLCI) cases was reported as 68% (relative risk 0.32, 95% CI 0.17–0.63, P-value not stated), which decreased to 60% when considering the subset of unvaccinated subjects (relative risk 0.40, 95% CI 0.20–0.76, P = 0.004).48,49 It is important to note when comparing these results that epidemiological investigations showed that seasonal influenza vaccination may have provided only limited protection due to widespread circulation of variant A/Sydney/05/97(H3N2)-like viruses across the United States in 1997/98.48–50 In a separate study, protective efficacy was not demonstrated between groups of healthcare workers.48,51 Some evidence exists suggesting the protective efficacy of oseltamivir, where an approximate 75% reduction in SLCI cases was shown in a pooled analysis (relative risk 0.27, 95% CI 0.09–0.83, P = 0.21) and a separate study (relative risk 0.24, 95% CI 0.09–0.61, P-value not stated).48,52,53

Stronger RCT evidence of benefit is available for at-risk adults and patients aged 65 years and over. LaForce et al.54 reported a protective efficacy of 83% (relative risk 0.17, 95% CI 0.07–0.44, P < 0.001) with zanamivir prophylaxis in an ITT population of community-based adolescents and adults. In patients aged 65 years or older, the protective efficacy was 80% – although not statistically significant, possibly due to the small number of incident cases detected (relative risk 0.20, 95% CI 0.02–1.72, P-value not stated).

In a separate study of patients aged 65 years and over within a residential care setting, the protective efficacy of oseltamivir was 92% (relative risk 0.08, 95% CI 0.01–0.63, P = 0.002).48,55

In vaccinated subgroups, the effectiveness is not consistently lower, which suggests relatively poor clinical effectiveness of seasonal influenza vaccine in some populations. There were no studies identified that reported data on seasonal prophylaxis in children.34,55

Do neuraminidase inhibitors used for post-exposure prophylaxis in household contacts reduce the risk of seasonal influenza infection among close contacts?

Tappenden et al.48 reported a pooled analysis of four RCTs that studied the use of zanamivir for post-exposure prophylaxis of contacts in mixed (adults and children) households; a protective efficacy of 81% (relative risk 0.19, 95% CI 0.11–0.33, P = 0.93) was observed when therapy was started within 48 hours of initial contact, a figure consistent across the included studies. RCT evidence for oseltamivir shows a similar protective efficacy of 81% in contacts of all index cases (relative risk 0.19, 95% CI 0.08–0.45, P = 0.15) and 79% in contacts of influenza-positive index cases (relative risk 0.21, 95% CI 0.08–0.58, P = 0.13) measured by SLCI.48 Whilst these data did not reach statistical significance, the point estimate effect sizes described carry clinical significance. The pooled analysis by Halloran et al.56 reported a protective efficacy for zanamivir and oseltamivir of 75% and 81%, respectively, whilst Ng et al.57 reported a lower protective efficacy of 46% among household contacts who initiated oseltamivir prophylaxis within 24 hours of exposure to an index case.

Further observational data are available from outbreak settings in elderly residential homes and hospitals.49, 58–62 The estimates of protective efficacy are not as consistently high but add coherence because ‘real-life’ practical and logistic difficulties associated with outbreak identification, as well as the early application of control measures, are reflected in such reports. The rate of influenza vaccination also varied between the populations studied.

Neuraminidase inhibitors and 2009 pandemic influenza A(H1N1)

Chronology of key events and use of antivirals in the UK

Cases of ILL and pneumonia, as well as a number of deaths associated with a novel strain of influenza, were first reported on 18 March 2009 in Mexico. WHO raised the influenza pandemic alert to Phase 4 on 27 April and Phase
the UK public health strategy shifted towards focusing on the pandemic alert to Phase 6 on 11 June. On 2 July 2009, the UK and worldwide, which contributed to WHO raising large outbreaks and sporadic cases were reported within progress, evidence of widespread community transmission, increased during May and June. As the pandemic progressed, evidence of widespread community transmission, large outbreaks and sporadic cases were reported within the UK and worldwide, which contributed to WHO raising the pandemic alert to Phase 6 on 11 June. On 2 July 2009, the UK public health strategy shifted towards focusing on treatment. Diagnosis was now made by clinical illness and not laboratory confirmation. Contacts of cases were only offered prophylaxis in special circumstances, and community-based antiviral collection points were opened to supply treatment to uncomplicated clinical cases, without direct physician involvement. Early experience from primary care showed that pandemic influenza usually produced mild self-limiting symptoms, although certain groups were at increased risk of serious illness. These groups included people with chronic diseases, patients who had received drug treatment for asthma during the past 3 years, pregnant women, adults aged 65 years and over and children aged under 5 years. Access to antiviral medication was to be prioritised for these groups, and treatment was recommended to start within 48 hours of symptoms onset. By September 2009, influenza activity in many Southern Hemisphere countries had declined considerably and returned to baseline threshold levels. Activity within Northern Hemisphere countries was more varied, and a second wave commonly occurred during autumn 2009; it was not until mid-December 2009 that all European countries appeared to pass the peak of their pandemic waves. In September 2010, WHO declared Phase 6 of the pandemic to be over and moved into the post-pandemic period. Pandemic vaccines only became available from October 2009 onwards; thus, antiviral drugs formed the mainstay pharmaceutical response for both pandemic waves and returned to baseline threshold levels. Activity within Southern Hemisphere countries had declined considerably, ranging from 1% to 12% that would appear to be lower than seasonal norms. A recent study based on the UK experience during its ‘containment’ response suggests that effectiveness in households was 92%.

What additional evidence has been generated regarding the effect of long-term prophylaxis and household-based post-exposure prophylaxis from studies related to the 2009 pandemic period?

None of the identified studies conducted during the 2009 pandemic period offered data on long-term prophylaxis. A small number of observational studies of post-exposure prophylaxis, without control groups, have noted secondary attack rates in households (or household-type settings) ranging from 1% to 12% that would appear to be lower than seasonal norms. A recent study based on the UK experience during its ‘containment’ response suggests that effectiveness in households was 92%.

Evidence of safety during the 2009 pandemic period

Donner et al. interrogated the Roche safety database (for oseltamivir) during the pandemic period from 1 May 2009 to 31 December 2009 (7482 adverse events reported in 4071 patients from an estimated 18.3 million treated), comparing this with pre-pandemic data (14900 events in 9537 patients from 64.7 million treated). Although 20 different adverse events showed a significant increase in incidence during the pandemic period, these were all attributable to infection with the novel pandemic virus for example, increases in the incidence of respiratory failure (odds ratio 4.71, 95% CI 2.11–10.5), staphylococcal infections (odds ratio 5.31, 95% CI 1.19–23.8) and spontaneous abortions (odds ratio 15.9, 95% CI 1.78–143), as previously
described. In contrast, the incidence of known side effects such as nausea and vomiting was not increased, whilst the incidence of neuropsychiatric events (odds ratio \(0.35, 95\% \text{ CI } 0.31–0.39\)) and diarrhoea (odds ratio \(0.40, 95\% \text{ CI } 0.28–0.57\)) during the pandemic both showed a statistically significant decline. These data suggest a benign safety profile during use in the 2009 pandemic, although troublesome levels of nausea were reported in some populations receiving prophylaxis.

**Implications for policy makers**

A number of findings from this review are relevant to policy makers. First, with regard to seasonal influenza, it is clear that the depth and quality of evidence diminishes as clinical outcomes increase in importance from symptom reduction, through complications, to hospitalisation and mortality. This is a true ‘evidence paradox’, and it reflects poorly on the scientific community that, 12 years post-licensure, these issues remain less than adequately clarified, due to financial barriers and logistic difficulties associated with conducting very large randomised trials with sufficient statistical power to address such questions. However, lack of evidence or poor-quality evidence of an effect should not be interpreted automatically to equate with evidence of no effect. It should be recognised that very large studies are needed to evaluate outcomes that are rare but of considerable public health importance; inevitably, these lie beyond the scope of RCTs.

Second, if a pandemic virus emerged in future which caused a high incidence of secondary bacterial complications, early treatment with oseltamivir and zanamivir may reduce the need for antibiotic use following clinically diagnosed influenza. Observational studies suggest that treatment may be of wider benefit in reducing a broader range of complications. Whilst it should be acknowledged that these observational data offer weaker evidence, their importance warrants careful consideration. Although these data should be interpreted with caution, preparedness plans for a novel highly virulent virus which increases the incidence of hospitalisation and pneumonia may still conclude that the use of NAIs should be recommended for the prevention of relevant complications. Indeed, as judged by the timing of availability of dedicated pandemic vaccines in 2009, it could be assumed that NAIs will again form the mainstay pharmaceutical response in future pandemics unless there are radical changes in vaccine manufacturing technology. In addition, if evidence from new publications from the 2009 pandemic period continues to show a benefit of early treatment with NAIs, the importance of enabling rapid access to available antiviral drug therapy during a pandemic will be further highlighted.

Long-term prophylaxis with NAIs may be of limited utility to preparedness plans due to pragmatic and logistic issues (including difficulties with implementation at population level and associated costs), except in high-risk situations where vaccine availability is delayed or response to vaccination is doubtful. However, preparedness plans should consider the solid evidence for the preventive efficacy of household-based post-exposure prophylaxis with NAIs; this control measure may not suit all national settings, but clearly possesses significant utility in reducing secondary cases within households when efficiently implemented.

**Recent developments and areas for further research**

Our rapid review identified the literature published to 30 June 2010, before the post-pandemic period was declared by WHO. The quantity of the evidence from the pandemic is likely to have grown following this date, although it is unlikely that the quality will have dramatically increased because experimental trials during a pandemic are both ethically and logistically challenging. Nevertheless, an increase in the number and size of observational studies presents the opportunity for a systematic review and meta-analysis of these data. In particular, analyses that seek to study public health outcome measures such as complications, hospitalisation and mortality will contribute substantially to the literature. Hsu et al. recently published one such review, including seasonal and 2009 pandemic data, which gauged the effectiveness and safety of antivirals for the treatment of influenza. The authors report that oseltamivir may reduce mortality, hospitalisation and symptom duration compared to no therapy in high-risk populations and earlier treatment may typically be associated with improved patient outcomes; zanamivir may similarly reduce hospitalisations and symptom duration, but potentially increase the risk of complications. Whilst the systematic review by Hsu et al. provides significant original findings which add to the literature, the study is, like others, limited by numerous caveats due in part to weakness in the published evidence from observational studies. We advocate that pooled analyses based on patient-level data are now needed to determine how effective NAIs were during the 2009 pandemic, and thereby might be in the next.

**Acknowledgements**

An earlier version of this review was endorsed by the Health Protection Agency’s Influenza and Respiratory Virus Programme Board. The final full report on which this manuscript is based was reviewed and endorsed by the
UK Scientific Pandemic Influenza Advisory Committee of which JSN-V-T is a member. The authors wish to thank both these committees for their comments. We thank, in particular, Dr James McMenamin (Health Protection Scotland), Professor Nick Phin and Dr Nick Gent (Health Protection Agency) for helpful comments on earlier versions of the full report.

Author contributions

NA and JSN-V-T involved in review concept and design; NA, CRB, RS, RP, GA, SK, RH, RC, SL and JE involved in critical appraisal and acquisition of data; NA, CRB and JSN-V-T involved in analysis and interpretation of data. CRB, RS, NA, RP, AC, AK, MZ and JSN-V-T involved in manuscript preparation and contribution of intellectual content; All authors have read and approved the final manuscript.

Conflicts of interest

The University of Nottingham Health Protection and Influenza Research Group is currently in receipt of research funds from GSK. The group has recently accepted an unrestricted educational grant for influenza research from F. Hoffmann-La Roche. Research on influenza funded by an unrestricted educational grant from AstraZeneca is also underway. The aforementioned funding received from GSK, F. Hoffmann-La Roche and AstraZeneca did not support any aspect of this work. JSN-V-T has received funding to attend influenza-related meetings, lecture and consultancy fees and research funding from several influenza antiviral drug and vaccine manufacturers. All forms of personal remuneration ceased in September 2010, but departmental funding for influenza-related research from GlaxoSmithKline plc, F. Hoffmann-La Roche and AstraZeneca remains current. He is a former employee of SmithKline Beecham plc. (now GlaxoSmithKline), Roche Products Ltd and Aventis-Pasteur MSD (now Sanofi-Pasteur MSD), all prior to 2005, with no outstanding pecuniary interests by way of shareholdings, share options or accrued pension rights. NA holds ordinary shares in GlaxoSmithKline plc; RP is currently undertaking research that is part-funded by GlaxoSmithKline plc; JE received a one-off honorarium from GlaxoSmithKline plc in 2008. The Health Protection Agency receives funding from a variety of vaccine manufacturers (GSK, Novartis, Crucell, Baxter, CSL) for specialist analysis of pandemic influenza vaccine clinical trials. MZ has served as the co-chair of the international expert Neuraminidase Inhibitor Susceptibility Network (NISN) group (1999–2010), comprising public health, academic and virology experts established to develop methodology and initiate global surveillance of antiviral resistance, and is a member of the WHO expert advisory group on antivirals. MZ is a member of the ISIRV Antiviral Group.

No other authors have declared potential conflicts.

Funding disclosure

The full report on which this manuscript is based was requested by the Department of Health, England, in April 2010 and funded jointly by the Health Protection Agency (HPA) and the Department of Health, England. The views expressed in this manuscript are those of the authors and do not necessarily reflect the views or official positions of either the Health Protection Agency or the Department of Health, England.

References

1. Nguyen-Van-Tam JS. Zanamivir for influenza: a public health perspective. BMJ 1999; 319:655–656.
2. Boseley S. GPs told not to prescribe new flu drug. The Guardian. 1999. Available at: http://www.guardian.co.uk/uk/1999/oct/09/sarahboseley. (Accessed 30 November 2011).
3. BBC. NHS agenda for expensive drugs. 1999. Available at: http://news.bbc.co.uk/1/hi/health/413566.stm. (Accessed 30 November 2011).
4. Hayden FG, Pavia AT. Antiviral management of seasonal and pandemic influenza. J Infect Dis 2006; 194(Suppl.1):S119–S126.
5. Godlee F. We want raw data, now. BMJ 2009; 339:b5405.
6. European Centre for Disease Prevention and Control. Public Health use of Influenza Antivirals During Influenza Pandemics. Stockholm; 2009.
7. National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 168. Amantadine, Oseltamivir and Zanamivir for the Treatment of Influenza. London: National Institute for Health and Clinical Excellence; 2009.
8. National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 158. Oseltamivir, Amantadine (review) and Zanamivir for the Prophylaxis of Influenza. London: National Institute for Health and Clinical Excellence; 2008.
9. Burch J, Faulden M, Conti S et al. Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation. Health Technol Assess 2009; 13:1–265.
10. World Health Organization. Pandemic Influenza Preparedness and Response: A WHO Guidance Document. Geneva; 2009.
11. World Health Organization. Comparative Analysis of National Pandemic Influenza Preparedness Plans. Geneva; 2011.
12. Donner B, Bader-Weder S, Schwarz R et al. Safety profile of oseltamivir during the 2009 influenza pandemic. Pharmacoepidemiol Drug Saf 2011; 20:532–543.
13. Atkins CY, Patel A, Taylor TH et al. Estimating effect of antiviral drug use during pandemic (H1N1) 2009 outbreak, United States. Emerg Infect Dis 2011; 17:1591–1598.
14. Department of Health. Use of Antivirals in an Influenza Pandemic. London; 2011:1–317. Available at http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_125328.pdf.
15. Meindl P, Bodo G, Palese P, Schulman J, Tuppy H. Inhibition of neuraminidase activity by derivatives of 2-deoxy-2,3-dehydro-N-acetyleneuraminic acid. Virology 1974; 58:457–463.
16. Palese P, Schulman JL, Bodo G, Meindl P. Inhibition of influenza and parainfluenza virus replication in tissue culture by 2-deoxy-2,3-dehydro-N-trifluoroacytelyneuraminic acid (FANA). Virology 1974; 59:490–498.

17. Palese P, Compan R. Inhibition of influenza virus replication in tissue culture by 2-deoxy-2,3-dehydro-N-trifluoroacytelyneuraminic acid (FANA): mechanism of action. J Gen Virol 1976; 33:159–163.

18. Colman PM, Varghese JN, Laver WG. Structure of the catalytic and antigenic sites in influenza virus neuraminidase. Nature 1983; 303:41–44.

19. von Itzstein M, Wu WW, Kok GB et al. Rational design of potent sialidase-based inhibitors of influenza virus replication. Nature 1993; 363:418–423.

20. Kim CU, Lev W, Williams MA et al. Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carboxyclic sialic acids analogues with potent anti-influenza activity. J Am Chem Soc 1997; 119:681–690.

21. Monto AS. Editorial commentary: viral susceptibility and the choice of influenza antivirals. Clin Infect Dis 2008; 47:346–348.

22. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. J Antimicrob Chemother 1999; 44(Suppl. B):23–29.

23. Dutkiewicz R. Oseltamivir in seasonal influenza: cumulative experience in low- and high-risk patients. J Antimicrob Chemother 2010; 65(Suppl. 2):i11–i24.

24. DataPharm. Summary of Product Characteristics - Tamiflu 75mg hard capsule. The electronic Medicines Compendium. 2011. Available at: http://www.medicines.org.uk/emc/medicine/10446/SPC/. (Accessed 31 December 2011).

25. GlaxoSmithKline UK. Relenza 5mg/dose inhalation - Summary of Product Characteristics (SPC) - electronic Medicines Compendium (eMC). 2011. Available at: http://www.medicines.org.uk/EMC/medicine/2608/SPC/Relenza+5mg+dose+inhalation+powder. (Accessed 31 December 2011).

26. Roche Products Limited. Tamiflu 75mg hard capsule - Summary of Product Characteristics (SPC) - electronic Medicines Compendium (eMC). 2011. Available at: http://www.medicines.org.uk/EMC/medicine/2608/SPC/Tamiflu+75mg+hard+capsule. (Accessed 14 December 2011).

27. Singh S, Barghoom J, Bagdonas A et al. Clinical benefits of oseltamivir in treating influenza in adult populations: results of a pooled and subgroup analysis. Clin Drug Invest 2003; 23:561–569.

28. Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. Arch Intern Med 2001; 161:212–217.

29. Deng W, Li Q, Zhong N. A multicenter study of efficacy and safety of oseltamivir in the treatment of suspected influenza patients. Zhonghua Yi Xue Za Zhi. 2004; 84:2132–2136.

30. Hedrick JA, Barzilai A, Behre U et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. Pediatr Infect Dis J. 2000; 19:410–417.

31. Whitley RJ, Hayden FG, Reisinger KS et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J. 2001; 20:127–133.

32. Nordstrom BL, Sung I, Suter P, Szene P. Risk of pneumonia and other complications of influenza-like illness in patients treated with oseltamivir. Curr Med Res Opin 2005; 21:761–768.

33. Barr CE, Schulman K, Iacuzzo D, Bradley JS. Effect of oseltamivir on the risk of pneumonia and use of health care services in children with clinically diagnosed influenza. Curr Med Res Opin 2007; 23:523–531.

34. Lee N, Chan PKS, Choi KW et al. Factors associated with early hospital discharge of adult influenza patients. Antivir Ther 2007; 12:501–508.

35. Enger C, Nordstrom BL, Thakrar B, Sacks S, Rothman KJ. Health outcomes among patients receiving oseltamivir. Pharmacoeconom Drug Saf 2004; 13:227–237.

36. Peters PH, Moscona A, Schulman KL, Barr CE. Study of the impact of oseltamivir on the risk for pneumonia and other outcomes of influenza, 2000-2005. Medscape J Med. 2008; 10:131.

37. Blumentals WA, Schulman KL. Impact of oseltamivir on the incidence of secondary complications of influenza in adolescent and adult patients: results from a retrospective population-based study. Curr Med Res Opin 2007; 23:2961–2970.

38. Cussells SW, Granger E, Kress AM et al. Use of oseltamivir after influenza infection is associated with reduced incidence of recurrent adverse cardiovascular outcomes among military health system beneficiaries with prior cardiovascular diseases. Circ Cardiovasc Qual Outcomes 2009; 2:108–115.

39. Gums JG, Pelletier EM, Blumentals WA. Oseltamivir and influenza-related complications, hospitalization and healthcare expenditure in healthy adults and children. Expert Opin Pharmacother 2008; 9:151–161.

40. Orzech EA, Shi N, Blumentals WA. Oseltamivir and the risk of influenza-related complications and hospitalizations in patients with diabetes. Clin Ther 2007; 29:2246–2255.

41. Madjid M, Curkendall S, Blumentals WA. The influence of oseltamivir treatment on the risk of stroke after influenza infection. Cardiology 2009; 113:98–107.

42. Chemaly RF, Ghosh S, Bodey GP et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine (Baltimore). 2006; 85:278–287.

43. Chemaly RF, Torres HA, Aguilara EA et al. Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. Clin Infect Dis 2007; 44:964–967.

44. McGeer A, Green KA, Plevneshi A et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007; 45:1568–1575.

45. Lee N, Choi KW, Chan PKS et al. Outcomes of adults hospitalised with severe influenza. Thorax 2010; 65:510–515.

46. Hanshaw-Porukul W, Simmerman JM, Naruoenijarakul U et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. PLoS One 2009; 4:e6051.

47. Piedra PA, Schulman KL, Blumentals WA. Effects of oseltamivir on influenza-related complications in children with chronic medical conditions. Pediatrics 2009; 124:170–178.

48. Tappenden P, Jackson R, Cooper K et al. Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation. Health Technol Assess 2009; 13:1–246.

49. Monto AS, Robinson DP, Herlocker ML et al. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. JAMA 1999; 282:31–35.

50. Centers for Disease Control and Prevention. Update: influenza activity – United States, 1997–98 season. MMWR Morb Mortal Wkly Rep 1998; 47:196–200.

51. GlaxoSmithKline Pharmaceuticals. Drugs for the prophylaxis of influenza – review of zanamivir, 2007.
Neuraminidase inhibitors for influenza

prophylaxis against influenza – placebo-controlled double-blind multicenter phase III trial. Kanshôgakü Zasshi 2000; 74:1062–1076.

53 Hayden FG, Atmar RL, Schilling M et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 1999; 341:1336–1343.

54 LaForce C, Man CY, Henderson RW et al. Efficacy and safety of inhaled zanamivir in the prevention of influenza in community-dwelling, high-risk adult and adolescent subjects: a 28-day, multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther 2007; 29:1579–1590.

55 Peters PH, Gravenstein S, Norwood P et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc 2001; 49:1025–1031.

56 Halloran ME, Hayden FG, Yang Y, Longini IM, Monto AS. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. Am J Epidemiol 2007; 165:212–221.

57 Ng S, Cowling BJ, Fang V et al. Effects of oseltamivir treatment on duration of clinical illness and viral shedding and household transmission of influenza virus. Clin Infect Dis 2010; 50:707–714.

58 Shinjoh M, Sato S, Sugaya N et al. Effect of post-exposure prophylaxis with oseltamivir for those in contacts with influenza patients in pediatric wards. Kanshôgakü Zasshi. 2004; 78:262–269.

59 Ambrozaitis A, Gravenstein S, van Essen GA et al. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population. J Am Med Dir Assoc 2005; 6:367–374.

60 Hirji Z, O’Grady S, Bonham J et al. Utility of zanamivir for chemoprophylaxis of concomitant influenza A and B in a complex continuing care population. Infect Control Hosp Epidemiol 2002; 23:604–608.

61 Bush KA, McNulty J, McPheie K et al. Antiviral prophylaxis in the management of an influenza outbreak in an aged care facility. Commun Dis Intell 2004; 28:396–400.

62 Chik KW, Li CK, Chan PKS et al. Oseltamivir prophylaxis during the influenza season in a paediatric cancer centre: prospective observational study. Hong Kong Med J 2004; 10:103–106.

63 World Health Organization. Evolution of a pandemic. 2010.

64 NHS Flu Resilience Team. Swine flu pandemic: from containment to treatment. Guidance for the NHS. 2009.

65 European Centre for Disease Prevention and Control. The 2009 A/H1N1 pandemic in Europe. Stockholm, 2010.

66 World Health Organization. H1N1 in post-pandemic period. Media statement, 2010. Available at: http://www.who.int/mediacentre/news/statements/2010/h1n1_vpc_20100810/en/index.html.

67 Boutouleau D, Houhou N, Deback C, Agut H, Brun-Vezinet F. Effects of early oseltamivir therapy on viral load in patients infected with pandemic (H1N1) 2009, United Kingdom. Emerg Infect Dis 2010; 16:351–352.

68 Cao B, Li X-W, Mao Y et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009; 361:2507–2517.

69 Ling LM, Chow AL, Lye DC et al. Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. Clin Infect Dis 2010; 50:963–969.

70 To KK, Chan K-H, Li IWS et al. Viral load in patients infected with pandemic H1N1 2009 influenza A virus. J Med Virol 2010; 82:1–7.

71 Xiao H, Lu S, Ou Q, Chen Y, Huang S. Hospitalized patients with novel influenza A (H1N1) virus infection: Shanghai, June - July 2009. Chin Med J 2010; 123:401–405.

72 Redelman-Sidi G, Sepkowitz KA, Huang CK et al. 2009 H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. J Infect 2010; 60:257–263.

73 Tsalik EL, Hendeshot EF, Sangvai DG et al. Clinical presentation and response to treatment of novel influenza A H1N1 in a university-based summer camp population. J Clin Virol 2010; 47:286–288.

74 Komiya N, Gu Y, Kamiya H et al. Clinical features of cases of influenza A (H1N1)v in Osaka prefecture, Japan, May 2009. Euro Surveill. 2009;14.

75 Grijalva-Otero I, Talavera JO, Solorzano-Santos F et al. Critical analysis of deaths due to atypical pneumonia during the onset of the influenza A (H1N1) virus epidemic. Arch Med Res 2009; 40:662–668.

76 Kwan-Gott TS, Baer A, Duchin JS. Spring 2009 H1N1 influenza outbreak in King County, Washington. Disaster Med Public Health Prep 2009; 3(Suppl. 2):S109–S116.

77 Siston AM, Rasmussen SA, Honein MA et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303:1517–1525.

78 Louie JK, Acosta M, Jamieson DJ, Honein MA. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2010; 362:27–35.

79 Creanga AA, Johnson TF, Graitter SB et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. Obstet Gynecol 2010; 115:717–726.

80 Denholm JT, Gordon CL, Johnson PD et al. Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia. Med J Aust 2010; 192:84–86.

81 Perez-Padilla R, de La Rosa-Zamboni D, Ponce De Leon S et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009; 361:680–689.

82 Miller RR, Markewitz BA, Rolfs RT et al. Clinical findings and demographic factors associated with ICU admission in Utah due to novel 2009 influenza A(H1N1) infection. Chest 2010; 137:752–758.

83 Chien Y-S, Su C-P, Tsai H-T et al. Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan. J Infect 2010; 60:168–174.

84 Rello J, Rodríguez A, Ibáñez P et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care 2009; 13:R148.

85 Domínguez-Cherit G, Lapinsky SE, Macias AE et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. JAMA 2009; 302:1880–1887.

86 Donaldson LJ, Rutter PD, Ellis BM et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 2009; 339:b5213.

87 Lee EH, Wu C, Lee EU et al. Fatalities associated with the 2009 H1N1 influenza A virus in New York city. Clin Infect Dis 2010; 50:1498–1504.

88 Louie JK, Acosta M, Winter K et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 2009; 302:1896–1902.

89 Dill CE, Favata MA. Novel influenza A (H1N1) outbreak on board a US navy vessel. Disaster Med Public Health Prep 2009; 3(Suppl. 2):S117–S120.

90 Kimberlin DW, Escude J, Gantner J et al. Targeted antiviral prophylaxis with oseltamivir in a summer camp setting. Arch Pediatr Adolesc Med 2010; 164:323–327.

91 Odaia F, Takahashi H, Toyokawa T et al. Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May-June 2009. Euro Surveill 2009; 14:pii: 19320.

92 Pebody RG, Harris R, Kafatos G et al. Use of Antiviral Drugs to Reduce Household Transmission of pandemic (H1N1) 2009, United Kingdom. Emerg Infect Dis 2011; 17:990–999.

93 Pierce M, Kurinzzuk JJ, Spark P, Brocklehurst P, Knight M. Perinatal outcomes after maternal 2009/H1N1 influenza: national cohort study. BMJ 2011; 342:d3214.
Bloom-Feshbach K, Simonsen L, Viboud C et al. Natality decline and miscarriages associated with the 1918 influenza pandemic: the Scandinavian and United States experiences. J Infect Dis 2011; 204:1157–1164.

Strong M, Burrows J, Redgrave P. A/H1N1 pandemic. Oseltamivir’s adverse events. BMJ 2009; 339:b3249.

Wallensten A, Oliver I, Lewis D, Harrison S. Compliance and side effects of prophylactic oseltamivir treatment in a school in South West England. Euro Surveill 2009; 14:19285.

Broadbent AJ, Subbarao K. Influenza virus vaccines: lessons from the 2009 H1N1 pandemic. Curr Opin Virol 2011; 1:254–262.

Conway JM, Tuite AR, Fisman DN et al. Vaccination against 2009 pandemic H1N1 in a population dynamical model of Vancouver, Canada: timing is everything. BMC Public Health 2011; 11:932.

Hsu J, Santesso N, Mustafa R et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012; 156:512–524.