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Original Article

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

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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.

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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-

cal benefit, their availability raised concerns in the UK about 'unnecessary' healthcare costs and increased pressure on family doctors resulting from people seeking treatment for influenza-like illness (ILI), where hitherto many with mild symptoms would have self-medicated with over-the-counter (OTC) preparations, or sought no treatment at all.[1–3]

Subsequently, the worldwide use of NAIs for treating seasonal influenza has been generally low and geographically patchy. This may be explained by a number of factors including uncertainty of the value of modest symptom reduction (especially in countries where health care is government-funded), the effect on clinical and public health outcomes (such as complications, hospitalisations and mortality) and controversies about the robustness of the evidence base for effectiveness in general.[4,5] A notable exception is Japan, where NAIs have been widely prescribed since their launch, especially to treat symptomatic children.[6] In the UK, use of NAIs for seasonal influenza in the National Health Service has been tightly constrained by guidance from the National Institute for Health and Clinical Excellence which effectively limits treatment usage to at-risk patients and post-exposure prophylaxis (PEP) to those at-risk and unvaccinated.[7–9]

The evidence base leading to licensure of NAIs was derived entirely from the study of seasonal influenza, which may not always be generalisable to a novel pandemic virus, such as a future severe pandemic arising from influenza A(H5N1). Pandemic policy makers have a particular interest in NAIs in terms of evidence of their effectiveness to reduce the public health impact of a future pandemic. In 2009, the World Health Organization (WHO) published guidance recommending the use of NAIs in the containment and treatment stages of an influenza pandemic, predicated on the pre-establishment of national stockpiles.[10] Prior to the 2009 pandemic, a review of national preparedness plans (n = 110) found that 61% of countries intended to use antivirals for the treatment of influenza and 76% for limited prophylaxis. Priority groups for prophylaxis were commonly healthcare and essential workers, contacts of symptomatic cases and certain at-risk patients.[11] An analysis of oseltamivir safety data published by F. Hoffman-La Roche Ltd estimated that 18·3 million individuals worldwide received the drug during the pandemic period 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.[13]

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 2-deoxy-2,3-dehydro-*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,[25,26] the use of oseltamivir should be based on an individual risk-benefit assessment by the attending physician.[26] 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.[25,26]

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.*[9] 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.[9] 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.[9]

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.[9] 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.[9]

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.[9]

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.[9] 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.[9]

The additional pooled analyses and observational studies we identified showed similar findings to Burch *et al.*[9] However, Lalezari *et al.*[28] and Singh *et al.* [27] 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, $P = 0{\cdot}015$) and ITTI healthy adults treated with oseltamivir (median difference 23·9 hours, $P < 0{\cdot}0001$), respectively. Singh *et al.*[27] also reported a significant reduction in time to perform normal daily activities following treatment with oseltamivir (median difference 46·4 hours, $P < 0{\cdot}0001$).

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.*[9] 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, $P < 0{\cdot}001$). This analysis was, however, strongly influenced by a trial undertaken by Deng *et al.*[29] 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, $P = 0{\cdot}05$).[9] 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.*[9] 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, $P = 0{\cdot}0009$). Evidence

Table 1. Clinical effectiveness of zanamivir (data adapted from Ref.9)

Subgroup	ITT population			ITTI population		
	No. trials	WMD (95% CI)	*P*-value	No. trials	WMD (95% CI)	*P*-value
Number of days to alleviation of symptoms						
Healthy adults	6	−0·57 (−1·07 to −0·08)	0·02	6	−0·96 (−1·38 to −0·54)	<0·0001
At-risk adults	6	−0·95 (−1·83 to −0·07)	0·03	5	−1·70 (−2·71 to −0·69)	0·0004
Elderly patients	5	−1·13 (−2·90 to 0·63)	0·21	5	−1·85 (−4·77 to 1·07)	0·21
All children	2	−0·94 (−1·43 to −0·46)	0·0001	1	−1·00 (−1·60 to −0·40)	N/S
Healthy children	1	−1·00 (−1·50 to −0·50)	N/S	1	−1·00 (−1·59 to −0·41)	0·0008
At-risk children	1	−2·00 (−6·94 to 2·94)	0·43	1	−3·75 (−7·59 to 0·09)	0·06
All at-risk	6	−0·98 (−1·84 to −0·11)	0·03	6	−1·83 (−2·81 to −0·86)	0·0002
Number of days to return to normal activity						
Healthy adults	7	−0·37 (−0·84 to 0·09)	0·11	7	−0·39 (−0·84 to 0·06)	0·09
At-risk adults	5	−1·07 (−2·81 to 0·68)	0·23	6	−1·77 (−4·40 to 0·86)	0·19
Elderly patients	–	–	–	1	−2·75 (N/S)	N/S
All children	1	−0·50 (−1·25 to 0·25)	N/S	1	−0·50 (−1·35 to 0·35)	N/S
Healthy children	1	−0·50 (−1·26 to 0·26)	N/S	1	−0·50 (−1·36 to 0·36)	N/S
At-risk children	1	−1·00 (−3·46 to 1·46)	0·43	1	−2·50 (−4·37 to −0·63)	0·009
All at-risk	6	−0·96 (−2·32 to 0·41)	0·17	6	−1·89 (−3·95 to 0·17)	0·07

WMD, weighted median difference; CI, confidence interval; ITT, intention-to-treat clinically diagnosed influenza; ITTI, intention-to-treat laboratory-confirmed influenza; N/S, not stated

Table 2. Clinical effectiveness of oseltamivir (data adapted from Ref. 9)

Subgroup	ITT population			ITTI population		
	No. trials	WMD (95% CI)	*P*-value	No. trials	WMD (95% CI)	*P*-value
Number of hours to alleviation of symptoms						
Healthy adults	4	−13·29 (−23·15 to −3·43)	0·008	6	−22·19 (−37·32 to −7·07)	0·004
At-risk adults	2	−14·06 (−40·82 to 12·96)	0·30	2	−20·09 (−56·47 to 16·29)	0·28
Elderly patients	1	−10·00 (−45·05 to 25·05)	N/S	1	−24·90 (−68·77 to 18·97)	N/S
All children	2	−21·05 (−33·81 to −8·29)	0·001	2	−28·88 (−43·77 to −14·00)	0·0001
Healthy children	1	−21·00 (−35·79 to −6·21)	N/S	1	−36·00 (−53·51 to −18·49)	N/S
At-risk children	1	−21·20 (−46·45 to 4·05)	N/S	1	−10·40 (−38·63 to 17·83)	N/S
All at-risk	3	−17·84 (−36·20 to 0·52)	0·06	3	−14·04 (−36·34 to 8·26)	0·22
Number of hours to return to normal activity						
Healthy adults	3	−31·94 (−46·95 to −16·93)	<0·0001	3	−63·17 (−99·08 to −27·27)	0·0006
At-risk adults	5	−58·84 (−116·58 to −1·11)	0·05	5	−70·79 (−136·75 to −4·84)	0·04
Elderly patients	3	−98·07 (−170·98 to −25·16)	0·008	3	−73·68 (−151·20 to 3·84)	0·06
All children	2	−21·05 (−33·81 to −8·29)	0·001	2	−31·85 (−46·73 to −16·96)	<0·0001
Healthy children	1	−30·08 (−43·35 to −16·81)	N/S	1	−44·57 (−63·75 to −25·39)	N/S
At-risk children	1	−21·20 (−46·45 to 4·05)	N/S	1	−12·60 (−36·20 to 11·00)	N/S
All at-risk	5	−58·84 (−116·58 to −1·11)	0·05	6	−19·20 (−41·42 to 3·01)	0·09

WMD, weighted median difference; CI, confidence interval; ITT, intention-to-treat clinically diagnosed influenza; ITTI, intention-to-treat laboratory-confirmed influenza; N/S, not stated.

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, $P = 0·04$).[9]

In children, there is RCT evidence that zanamivir significantly reduces the likelihood of requiring antibiotics by 95% in ITT children treated for ILI (odds ratio 0·05, 95% CI 0·01–0·23, *P*-value not stated).[9,30] For oseltamivir, RCT

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 (ITTI).[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.[32,33,36,39,47] 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.[54,55]

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 ILI 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

5 3 days later following emerging evidence from numerous countries across the American continent that the virus was causing community-level outbreaks.[63] In the UK, the first laboratory-confirmed cases were identified in Scotland on 27 April 2009, after which the strategic approach adopted was that of containment.[64] In practice, early on this involved taking swabs for laboratory confirmation of suspected cases, advising self-isolation at home, collecting enhanced surveillance data on potential exposures, recommending antiviral treatment for the index case, contact tracing and recommending prophylaxis for close contacts. Despite best efforts, the incidence of influenza rapidly 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.[64] 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.[65] In September 2010, WHO declared Phase 6 of the pandemic to be over and moved into the post-pandemic period.[66] Pandemic vaccines only became available from October 2009 onwards; thus, antiviral drugs formed the mainstay pharmaceutical response for both pandemic waves in the UK and most other countries.

What additional evidence has been generated regarding the effect of treatment on duration of illness and complications from studies related to the 2009 pandemic period?

We identified no new pandemic-specific data that substantially add to or contradict the seasonal evidence base regarding the effect of antiviral drugs on duration of illness or symptoms. However, corroborative evidence is available suggesting that virus shedding (which may be a marker for symptom severity) was reduced by antiviral treatment.[67–72] In children, there are new observational data suggesting that early treatment reduced the duration of fever.[71,73,74]

Regarding complications, the strongest and most consistent theme emerging to date from the 2009 pandemic data is the effect in adults of early (generally within 48 hours) versus late initiation of treatment (because 'no treatment' comparators would have been unethical) in terms of reducing the likelihood of hospitalisation and requiring intensive care.[75–79] These data pertain to patients who were mainly young, including pregnant women, and are consistent with the epidemiology of the 2009 pandemic. The same effect was also observed in at-risk adult patients.[80–84] A small number of studies suggest that increased in-hospital mortality might be related to the late initiation of antiviral therapy.[85–88] It is acknowledged that further data are slowly emerging on this subject and that additional analyses are needed to evaluate the public health impact of different national policies for antiviral use during the 2009 pandemic.

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 1·8% to 12% that would appear to be lower than seasonal norms.[29–91] A recent study based on the UK experience during its 'containment' response suggests that effectiveness in households was 92%.[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).[12] 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.[93–94] 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% CI 0·31–0·39) and diarrhoea (odds ratio 0·40, 95% 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.[95,96]

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.[97,98] 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.*[99] 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.*[99] 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.

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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 Astra Zeneca is also underway. The aforementioned funding received from GSK, F. Hoffmann-La Roche and Astra Zeneca 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, 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.

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