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Oseltamivir, zanamivir and amantadine in the prevention of influenza: A systematic review

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Summary *Objective:* To systematically review evidence relating to the clinical efficacy of oseltamivir, zanamivir and amantadine in the prevention of influenza.
Methods: RCTs evaluating these interventions in seasonal prophylaxis and post-exposure prophylaxis were identified using electronic bibliographic databases and handsearching of retrieved articles.
Results: Oseltamivir was effective in preventing symptomatic laboratory-confirmed influenza (SLCI) in seasonal prophylaxis in healthy adults and at-risk elderly subjects and in post-exposure prophylaxis within households of mixed composition. Post-exposure prophylaxis using oseltamivir for paediatric contacts was observed to prevent SLCI. Zanamivir prevented SLCI in seasonal prophylaxis in healthy adults, at-risk adults and adolescents and in post-exposure prophylaxis within mixed households, with a trend for seasonal and post-exposure preventative effects in elderly subjects. Evidence for amantadine prophylaxis across subgroups was very limited. However, amantadine prevented SLCI in seasonal prophylaxis in healthy adults and in outbreak control amongst adolescent subjects. Interventions were reported to be well tolerated by subjects, with a relatively low proportion of subjects experiencing drug-related adverse events and drug-related withdrawals.
Conclusions: Evidence was identified for the efficacy of oseltamivir and zanamivir in preventing influenza in a range of population subgroups. The evidence base for amantadine was considerably more limited.

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Introduction

Influenza is a contagious, acute febrile respiratory infection caused by the influenza virus. Influenza A and B are responsible for nearly all influenza illness, with influenza A accounting for approximately 80% of outbreaks.[1] The level of influenza in a community is measured via a combination of the consultation rate for influenza-like illness (ILI) and the laboratory-based identification of influenza virus in samples from individuals with ILI.[2] Seasonal influenza generally occurs during the winter months in the northern hemisphere.[3] Worldwide pandemics occur infrequently when a new influenza subtype of avian or porcine origin crosses the species barrier, is transmissible from person-to-person, and differs antigenically from recently circulating human strains of influenza, so the population has little or no immunity to the new virus.

In healthy adults, seasonal influenza is often self-limiting and does not require treatment. However, complications such as pneumonia and exacerbations of asthma and chronic bronchitis can occur. Serious influenza-related complications are more common in individuals who are aged 65 years or over, who live in long-stay residential care facilities, or who have certain co-morbidities, including chronic respiratory, cardiovascular, renal, hepatic or neurological disease, diabetes, or immunosuppression.[3] Complications may require antibiotic treatment, hospitalisation, and are associated with increased mortality. Estimated numbers of deaths that occur each year in the UK due to influenza have ranged between 12,000 and 13,800 deaths, mainly among the elderly and individuals with co-morbidities.[4,5,6]

The objective of this systematic review, commissioned by the National Institute for Health and Clinical Excellence (NICE) as an update to previous guidance[7], was to evaluate the performance of the neuraminidase inhibitors oseltamivir and zanamivir and the M2 inhibitor amantadine in influenza prophylaxis. The scope of the NICE assessment covered two prophylactic circumstances: i) post-exposure prophylaxis and ii) seasonal prophylaxis. The populations analysed included children, adults and older people, with each group being further sub-divided into healthy individuals or those at-risk of developing complications of influenza. The review findings, together with a related health economic decision model, were used to inform the current NICE guidance on the use of antiviral drugs in seasonal and post-exposure influenza prophylaxis.[8,9]

Methods

Identification of evidence

A review protocol outlining the planned approaches to the review was developed and adhered to throughout the conduct of the review. The search strategy consisted of the following approaches: searching of electronic databases (searched August 2007 and updated in August 2009); contact with topic experts; and handsearching of bibliographies of retrieved papers. Searches were performed in electronic databases including Medline, Medline in Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, BIOSIS, CINAHL, DARE, NHS EED and HTA databases, OHE HEED, NRR (National Research Register), Science Citation Index, Current Controlled Trials, Clinical Trials.gov. The search strategies included subject headings and free text terms, combined using Boolean logic, to identify all published and unpublished data relating to the clinical effectiveness of oseltamivir, zanamivir and amantadine in the prevention of influenza. Searches for the clinical effectiveness review were limited by publication type to controlled clinical trials, and systematic reviews. Searches were not restricted by the date of publication or by language. Published findings identified during this assessment are presented in this publication.

Study selection

Studies were considered eligible for inclusion if they related to the use of oseltamivir, zanamivir or amantadine administered in line with current UK marketing authorisations.[10] Population groups considered were children, adults and the elderly (see Tables 1–3 for age composition of study populations), with each group being further subdivided into healthy individuals or those at-risk of developing complications of influenza. Two prophylactic situations were assessed: i) seasonal prophylaxis, and ii) post-exposure prophylaxis. Interventions were compared against each other and against no prophylaxis (whereby subjects received any of the following: placebo, no treatment or expectant treatment following onset of symptomatic influenza). The number of influenza cases prevented was measured in terms of symptomatic, laboratory-confirmed influenza (SLCI) or, in the absence of this outcome, acute respiratory illness or influenza-like illness and/or confirmed influenza infection. Other outcomes of interest included complications prevented, hospitalisations prevented, length of influenza illness, time to return to normal activities, mortality, health-related quality of life, and adverse events. The following exclusion criteria were applied: intervention medications not used in accordance with their licensed indications, and studies only published in languages other than English. Studies based on experimentally-induced influenza are not described in this report due to limited generalisability to clinical practice. Based on the above inclusion/exclusion criteria, study selection was undertaken by one reviewer (RJ), with involvement of a second reviewer (KC/ES) when necessary to provide consensus on inclusion or exclusion of studies.

Data abstraction

Data was extracted by one reviewer (RJ) using a form developed for this purpose. All data abstraction was checked and confirmed by a second reviewer (KC).

Quality assessment

The quality of included randomised controlled studies was assessed using quality criteria based on those developed by the NHS Centre for Reviews and Dissemination.[11] Quality assessment was confirmed by a second reviewer (KC).

Table 1 Characteristics of included oseltamivir prophylaxis trials.

Trial and reference details	Population characteristics	Interventions (no. of patients in each arm)	Preventative strategy	Prophylaxis duration
WV15825; Peters *et al.*, 2001[61] De Bock *et al.*, 2000[82]	At-risk elderly subjects living in a residential home (Mean age = 81–82 yrs across treatment arms age 81 yr) (98% with concomitant disease in each group), Intervention arm: 80.4% vaccinated Placebo arm: 80.1% vaccinated	Intervention arm: Oseltamivir 75 mg once daily $n = 276$ Placebo arm: $n = 272$	Seasonal	6 weeks
WV15673; Hayden *et al.*, 1999[62]	Healthy unvaccinated adults aged 18–65 yrs living in the community. Conducted at study sites in Virginia, USA	Intervention arm: Oseltamivir 75 mg once daily $n = 268$ Placebo arm: $n = 268$	Seasonal	6 weeks
WV15697; Hayden *et al.*, 1999[62]	Healthy unvaccinated adults aged 18–65 yrs living in the community. Conducted at study sites in Texas and Kansas City, USA	Intervention arm: Oseltamivir 75 mg once daily $n = 252$ Placebo arm: $n = 251$	Seasonal	6 weeks
WV15799; Welliver *et al.*, 2001[59]	Subjects of mixed age and health status living in households. Adults and children aged 12 years and above (as contacts), Contacts of all index cases: Intervention arm: 11.4% vaccinated. Placebo arm: 13.9% vaccinated Index cases did not receive treatment.	Intervention arm: Oseltamivir 75 mg once daily $n = 493$ Placebo arm: $n = 462$	Post-exposure prophylaxis	7 days
WV16193; Hayden *et al.*, 2004[60]; Hayden *et al.*, 2002[83]; Belshe *et al.*, 2001[84]	Subjects of mixed age and health status. Adults and children aged 1 year and above. Contacts: Oseltamivir prophylaxis arm: 8% vaccinated Expectant treatment arm: 7% vaccinated Index cases in both arms received treatment with oseltamivir 75 mg twice daily for 5 days.	Oseltamivir: prophylaxis (PEP) vs. treatment on influenza onset (expectant treatment); index cases in both groups received treatment. Oseltamivir prophylaxis arm: Oseltamivir 75 mg daily for 10 days, $n = 410$ Expectant treatment arm: Oseltamivir treatment on influenza onset 75 mg twice daily for 5 days (less in children), $n = 402$ Subjects reported as $\leq$ 12 years Oseltamivir prophylaxis arm: $n = 69$, Expectant treatment arm: $n = 65$	Post-exposure prophylaxis	10 days

Data synthesis

Data were presented within a narrative synthesis. Where quantitative synthesis was considered to be appropriate, statistical meta-analysis was undertaken using a random effects model within Review Manager (RevMan) software (version 4.2.10, The Cochrane Collaboration) in order to calculate pooled estimates for relative risks for outcomes of interest. Efficacy data were presented as relative risks (RR) and protective efficacy (PE = 1 minus RR, expressed as a percentage) with associated 95% confidence intervals (95% CI).

The methods and findings of this review have been reported based on the PRISMA standards for systematic reviews and meta-analyses.[12]

Table 2 Characteristics of included zanamivir prophylaxis trials.

Trial and reference details	Population characteristics	Interventions (no. of patients in each arm)	Preventative strategy	Prophylaxis duration
NAIA3005; Monto *et al.*, 1999[72]	Healthy adults (aged 18—64 years) from University communities, Intervention arm: 14% vaccinated Placebo arm: 14% vaccinated	Intervention arm: Zanamivir 10 mg once daily $n = 553$ Placebo arm: $n = 554$	Seasonal	28 days
NAI30034; LaForce *et al.*, 2007[73]	At-risk adolescents and adults (aged 12 yrs and above). High-risk defined as age 65 yrs and above or having chronic disorders of pulmonary or cardiovascular system or diabetes mellitus. Intervention arm: 67% vaccinated Placebo arm: 68% vaccinated	Intervention arm: Zanamivir 10 mg once daily $n = 1678$ randomised, $n = 1595$ completed study Placebo arm: $n = 1685$ randomised, $n = 1594$ completed study Aged $\geq$65 years $n = 946$	Seasonal	28 days
NAI30031; Monto *et al.*, 2002[63]	Subjects of mixed age and health status. Adults and children aged 5 years and above (as contacts). Index cases: Intervention arm: 8% vaccinated, Placebo arm: 5% vaccinated, Contact cases: Intervention arm: 11% vaccinated, Placebo arm: 10% vaccinated Index cases did not receive treatment.	Intervention arm: Zanamivir 10 mg once daily $n = 661$ Placebo arm: $n = 630$	Post-exposure prophylaxis	10 days
NAI30010; Hayden *et al.*, 2000[64]	Subjects of mixed age and health status. Adults and children aged 5 years and above. Contacts: Intervention arm: 14% vaccinated, Placebo arm: 18% vaccinated Index cases were randomised to zanamivir twice daily or placebo.	Intervention arm: Zanamivir inhaled 10 mg daily $n = 414$ Placebo arm: $n = 423$	Post-exposure prophylaxis	10 days
NAIA2009, NAIB2009; Kaiser *et al.*, 2000[65]	Subjects of mixed age and health status. Unvaccinated adults and children aged 13—65 years (as contacts). Index cases did not receive treatment.	Intervention arm: Zanamivir 10 mg inhaled daily $n = 144$ Placebo arm: $n = 144$	Post-exposure prophylaxis	5 days
NAIA3004; Ambrozaitis *et al.*, 2005[66]; Ambrozaitis *et al.*, 2001[85]	At-risk elderly subjects in long-term care (mean age Intervention arm = 66.8 yrs, Placebo arm = 67.2 yrs) (84—85% at-risk of complications) Intervention arm: 9.6% vaccinated, Placebo arm: 8.8% vaccinated	Intervention arm: Zanamivir once daily $n = 242$ Placebo arm: $n = 252$	Outbreak control	14 days
NAIA3003; Gravenstein *et al.*, 2005[74]	At-risk elderly subjects in long-term care (mean age Intervention arm = 76.3 yrs, Placebo arm = 74.8 yrs) (96—100% at-risk of complications) Intervention arm: 99% vaccinated, Placebo arm: 92% vaccinated	Intervention arm: Zanamivir 10 mg once daily $n = 12$ for influenza B outbreak Placebo arm: Placebo $n = 13$ for influenza B outbreak	Outbreak control	14 days

Results

A total of 1010 citations were identified and, following removal of duplicate records, were screened for inclusion in the review.

Seven citations were excluded, since the full text article was not available in English.[13—19]

Thirty nine studies were excluded as they related to the use of intervention medications not in accordance with their UK licensed indications. The majority of these were specific to the use of amantadine,[20—51] whilst six were studies of zanamivir[52—57] and one related to oseltamivir.[58] Evidence for amantadine prophylaxis in children under 10 years is not presented in this systematic review, as such

Table 3 Characteristics of included amantadine prophylaxis trials.

Trial and reference details	Population characteristics	Interventions (no. of patients in each arm)	Preventative strategy	Prophylaxis duration
Reuman *et al.*, 1989[70]	Healthy unvaccinated adults aged 18—55 years living in the community	Intervention arm: Amantadine 100 mg/day $n = 159$ Placebo arm: $n = 159$	Seasonal	Presumed 6 weeks
Aoki *et al.*, 1986[71]	Healthy adults in a military setting, (age not defined) 6—8 individuals in each study year immunised against influenza in previous years	Intervention arm: Amantadine 100 mg/day, 1980—1981 $n = 74$, 1981—1982: under 28 yrs $n = 21$, over 29 yrs $n = 29$, 1982—1983 $n = 46$ Placebo arm: 1980—1981 $n = 48$, 1981—1982: under 28 yrs $n = 16$, over 29 yrs $n = 18$, 1982—1983 $n = 33$	Seasonal	39 days (1980—1981) 32 days (1982—1983)
Pettersson *et al.*, 1980[75]	Elderly subjects (mean ages Intervention arm = 77.4 yrs, Placebo arm = 79.0 yrs) living in a residential home, vaccination status unclear, but discussion states no adequate vaccine available	Intervention arm: Amantadine 100 mg/day, randomised $n = 94$, completing study $n = 89$ Placebo arm: randomised $n = 101$, completing study $n = 99$	Seasonal	9 weeks
Payler & Purdham, 1984[67]	Adolescent males (13—19 yrs old) in boarding school setting, 87% vaccinated	Intervention arm: Amantadine 100 mg/day randomised $n = 299$, final analysis $n = 267$ Comparison arm: No specific treatment randomised $n = 307$, final analysis $n = 269$	Outbreak control	14 days
Smorodintsev *et al.*, 1970a, b[68,69]	Male adults (recruitment pool aged 18—30 yrs) (presumed healthy) in semi-isolated engineering school populations	Intervention arm: Amantadine 100 mg/day (50.7% of 10,053), assigned to group $n = 5092$, onset of influenza prior to dosing $n = 441$, $n = 4559$ regularly or irregularly taking amantadine. Placebo arm: (31.6% of 10,053), assigned to group $n = 3175$, onset of influenza prior to dosing $n = 307$, $n = 2804$ receiving placebo (3175 minus 307 = 2868, 2804 included in analysis. Internal control arm: individuals at the same engineering schools as the amantadine and placebo groups, but living at home rather than at the school; received no prophylaxis (10.0% of 10,053) $n = 1011$ External control: individuals at an 8th engineering school; received no prophylaxis (7.7% of 10,053), assigned to group $n = 775$	Outbreak control	5 of 7 populations dosed for 30 days, 2 populations dosed for 12 days

data were excluded as amantadine dosage is not established in this age group according to licensed indications.

Twenty two published reports of 18 RCTs were included. Seven references comprising four full papers and three abstracts were identified for five RCTs describing the prophylactic use of oseltamivir (Table 1). For zanamivir, nine published reports of eight RCTs were identified, including seven full papers and two abstracts (see Table 2). We identified six papers reporting five RCTs evaluating the use of amantadine in the prevention of influenza (Table 3).

The quality of the oseltamivir prophylaxis evidence was considered robust in terms of study design and reporting. However, randomisation methods used and concealment of allocation were unclear in two study reports.[59,60] All oseltamivir studies were judged to have achieved baseline comparability amongst subjects. Four study reports listed potentially confounding co-interventions, including vaccination status[59–62], recent use of antivirals[60,61] and antibiotics.[60] For some studies, it was unclear whether outcome assessors,[59–62] intervention providers[59,61] or participants were blinded to treatment allocation,[59] whilst one study was described as being open-label in design.[60] All oseltamivir trials retained at least 80% of randomised subjects for analysis. The identified evidence for the use of zanamivir in prophylaxis against influenza had a lack of detail on methods of randomisation[63–65] and allocation concealment.[64–66] All zanamivir studies included over 80% of randomised subjects in analyses. Several limitations in the quality of the included studies relating to the prophylactic use of amantadine were noted. A lack of detail on methods of randomisation,[67–69] blinding,[67–71] and concealment of treatment allocation was observed.[67–69,71] Five study reports described co-interventions with the potential to affect outcomes, such as vaccination.[67–71]

Prevention of symptomatic, laboratory-confirmed influenza

The primary outcome reported in most included trials related to cases of influenza prevented as measured in terms of the incidence of SLCI. Key findings are summarised in Tables 4 and 5.

Use of oseltamivir in seasonal prophylaxis

Oseltamivir was efficacious in seasonal prophylaxis against SLCI in healthy adults (RR = 0.24, 95% CI 0.09–0.54, pooled estimate from two trials reported as a single publication).[62] A protective effect of oseltamivir in seasonal prophylaxis against SLCI was notable in one trial amongst the frail elderly living in residential care (98% with concomitant disease) (RR = 0.08, 95% CI 0.01–0.63).[61]

Use of oseltamivir in post-exposure prophylaxis

Oseltamivir conveyed a protective efficacy of 81% against SLCI in household contacts of mixed composition (adults and children aged 1 year and above, and adults and children aged 12 years and above) (RR = 0.19, 95% CI 0.08–0.45) (pooled estimate from two trials).[59,60] Only one RCT[60] in which data relating specifically to children aged 1–12 years were presented was identified. Post-exposure prophylaxis in paediatric contacts (aged 1 year and above) was demonstrated to have a preventative effect against SLCI in this trial (RR = 0.36, 95% CI 0.15–0.84).

Use of zanamivir in seasonal prophylaxis

Data were obtained from one trial demonstrating a protective efficacy of 68% for seasonal prophylaxis using zanamivir in healthy adults (RR = 0.32, 95% CI 0.17–0.63) (calculated by assessment group).[72] A further trial showed zanamivir to be effective in seasonal prophylaxis in at-risk adolescents and adults (RR = 0.17, 95% CI 0.07–0.44), with a non-significant preventative effect in older people

Table 4 Efficacy of interventions in seasonal prevention of symptomatic, laboratory-confirmed influenza.

Prophylactic strategy	Relative risk of developing symptomatic, laboratory-confirmed influenza (95%C.I.)		
	Amantadine	Oseltamivir	Zanamivir
Seasonal prophylaxis in healthy children	Dosage not established in children	NDA	NDA
Seasonal prophylaxis in at-risk children	Dosage not established in children	NDA	NDA
Seasonal prophylaxis in healthy adults	0.40 (0.08–2.03) (Reuman *et al.*, 1989)[70] From 1 trial	0.24 (0.09–0.54) (Hayden *et al.*, 1999)[62] From 2 trials	0.32 (calculated by assessment group) (0.17–0.63) (Monto *et al.*, 1999)[72] From 1 trial
Seasonal prophylaxis in at-risk adults and adolescents	NDA	NDA	0.17 (0.07–0.44) (LaForce *et al.*, 2007)[73] From 1 trial
Seasonal prophylaxis in healthy elderly subjects	No data reported (Pettersson *et al.*, 1980)[75]	NDA	0.20 (0.02–1.72) (LaForce *et al.*, 2007)[73] From 1 trial
Seasonal prophylaxis in at-risk elderly subjects	No data reported (Pettersson *et al.*, 1980)[75]	0.08 (0.01–0.63) (Peters *et al.*, 2001)[61] (98% subjects with concomitant disease) From 1 trial	0.20 (0.02–1.72) (LaForce *et al.*, 2007)[73] From 1 trial

(NDA indicates subgroup categories for which no data were available).

Table 5 Efficacy of interventions in post-exposure prevention of symptomatic, laboratory-confirmed influenza.

Prophylactic strategy	Relative risk of developing symptomatic, laboratory-confirmed influenza (95%C.I.)		
	Amantadine	Oseltamivir	Zanamivir
Post-exposure prophylaxis in mixed households	NDA	0.19 (0.08—0.45) (Hayden *et al.*, 2004)[60]; Welliver *et al.*, 2001)[59] From 2 trials	0.21 (0.13—0.33) (Hayden *et al.*, 2000;[64] Kaiser *et al.*, 2000;[65] Monto *et al.*, 2002)[63] From 4 trials
Post-exposure prophylaxis in healthy children	Dosage not established in children	0.36 (0.15—0.84) (Hayden *et al.*, 2004)[60] From 1 trial	NDA
Post-exposure prophylaxis in at-risk children	Dosage not established in children	NDA (subjects with a number of chronic conditions excluded) (Hayden *et al.*, 2004)[60]	NDA
Post-exposure prophylaxis in healthy adults and adolescents	0.10 (0.03—0.34) (Payler & Purdham, 1984)[67] From 1 trial	NDA	NDA
Post-exposure prophylaxis in at-risk adults and adolescents	NDA	NDA	NDA
Post-exposure prophylaxis in healthy elderly subjects	NDA	NDA	NDA
Post-exposure prophylaxis in at-risk elderly subjects	NDA	NDA	0.68 (0.33—1.27) (Ambrozaitis *et al.*, 2005)[66] (calculated by assessment group) (Subjects 85% at-risk of complications)

(NDA indicates subgroup categories for which no data were available).

(1/946 in zanamivir arm, 5/950 in placebo arm) (RR = 0.20, 95% CI 0.02—1.72).[73]

Use of zanamivir in post-exposure prophylaxis

Post-exposure prophylaxis using zanamivir was effective in preventing transmission of SLCI in households of mixed composition (adults and children aged 5 years and above,[63,64] unvaccinated adolescents and adults aged 13—65 years)[65] based on three publications (RR = 0.21, 95% CI 0.13—0.33).[63—65] Evidence for outbreak control in the elderly in long-term care was more limited, with a non-significant protective effect against SLCI demonstrated (RR = 0.68, 95% CI 0.33—1.27), whereby all cases occurred in unvaccinated subjects (calculated by assessment group).[66] Data for zanamivir versus placebo were limited in the study reported by Gravenstein *et al.*[74] since no subjects developed influenza during the study period and data were excluded from analysis in the published report.

Use of amantadine in seasonal prophylaxis

Owing to low attack rates during study periods, evidence for the use of amantadine against SLCI in seasonal prophylaxis was limited. One trial demonstrated a non-significant preventative effect among healthy adults in seasonal prophylaxis (RR = 0.40, 95% CI 0.08—2.03).[70] The use of amantadine in seasonal prophylaxis in healthy adults appeared to result in no difference in the incidence of acute respiratory illness between treatment groups.[71] No data were available relating to the efficacy or effectiveness of amantadine in seasonal prophylaxis in elderly subjects, since there was no evidence of an influenza epidemic among this group during the period of study.[75]

Use of amantadine in post-exposure prophylaxis

A study of outbreak control in a boarding school setting showed that amantadine was effective in preventing SLCI in healthy adolescents (RR = 0.10, 95% CI 0.03—0.34).[67] Only very limited evidence was available in the publications reported by Smorodintsev *et al.* (1970),[68,69] which indicated the role of amantadine in preventing (RR = 0.59, 95% CI 0.49—0.70) and shortening the duration ($p < 0.05$) and severity ($p < 0.01$) of clinical influenza. However, the reporting of this study was unclear.

Secondary outcomes

Limited data were reported relating to complications prevented, hospitalisations prevented, length of influenza illness and time to return to normal activities.

Use of oseltamivir in seasonal prophylaxis

One study[61] described the impact of oseltamivir prophylaxis on secondary complications of influenza (including bronchitis, pneumonia and sinusitis) and demonstrated that oseltamivir seasonal prophylaxis was associated with

a non-statistically significant 78% relative reduction in secondary complications (no further details presented) among at-risk elderly subjects with laboratory-confirmed influenza ($P = 1.14$, as reported).

Use of oseltamivir in post-exposure prophylaxis

In a study of post-exposure prophylaxis reported by Hayden *et al.*[60] and conducted in a population of mixed composition (adults and children aged 1 year and above), the proportion of contacts with laboratory-confirmed influenza with at least one secondary complication (including bronchitis, pneumonia, lower respiratory tract infection, otitis media or sinusitis) was broadly equivalent among post-exposure group subjects and those in the control arm who received expectant treatment upon the onset of influenza-like illness (7% (3/46) versus 5% (4/75)); however the more severe respiratory complications (bronchitis and pneumonia) occurred among the expectant treatment group.[60] The median duration of illness in contacts was shorter in the oseltamivir post-exposure prophylaxis group ($n = 10$) versus those receiving treatment on influenza onset ($n = 33$) (5.5 h (range 0—87) versus 39.8 h (range 0—627) ($P = 0.103$)).[60] Similarly, fewer contacts with laboratory-confirmed influenza in the oseltamivir post-exposure prophylaxis group were bed-bound compared with subjects in those receiving treatment on influenza onset (7% (3/46) versus 28% (21/75)), demonstrating a milder form of disease.[60]

Use of zanamivir in seasonal prophylaxis

A conference abstract provided additional data on the impact of zanamivir seasonal prophylaxis on secondary outcomes.[76] Significantly less work absence was reported among subjects who received zanamivir as seasonal prophylaxis versus control group subjects (mean hours lost 0.6 vs 1.4, $P = 0.001$). Total productive time lost was also less in the zanamivir group (1.8 vs. 3.0 h, $P = 0.001$).

Use of zanamivir in post-exposure prophylaxis

Significantly fewer households randomised to zanamivir post-exposure prophylaxis reported a contact developing a complication of laboratory-confirmed influenza (2% vs. 6%, $P = 0.01$).[63] Complications of SLCI (defined as adverse events consistent with complications of influenza among subjects with SLCI) during the first 28 days following post-exposure prophylaxis initiation were slightly lower among the zanamivir-treated subjects versus placebo, although this difference was not statistically significant (5% vs. 6%, $P = 0.653$).[66] This study was powered for the primary outcome of protective efficacy, rather than such secondary outcomes. The proportion of cases with complications requiring antibiotics was marginally lower among subjects receiving zanamivir post-exposure prophylaxis compared with placebo (5% vs. 8%, statistical significance not reported).[64] Furthermore, among household contacts with laboratory-confirmed influenza, the median time to alleviation of symptoms without use of medication was 5.5 days in the prophylaxis and 8.0 days in the placebo groups (statistical significance not reported).[64] Mean duration of significant influenza-like symptoms was also observed to be shorter in the zanamivir post-exposure prophylaxis versus placebo group (0.2 vs. 0.6 days, $P = 0.016$).[65]

Use of amantadine in seasonal prophylaxis

No secondary outcomes were described relating to the use of amantadine in seasonal prophylaxis.

Use of amantadine in post-exposure prophylaxis

Limited evidence was identified for milder influenza illness of shorter duration as a result of the use of amantadine in post-exposure prophylaxis.[68,69] Of 400 randomly selected participants, the severity of symptoms was reported as 56.0% mild and 9.0% severe in the amantadine group, and 38.0% mild and 19.0% severe in the placebo group ($p < 0.01$ for severe symptoms, $p < 0.001$ for mild symptoms (no further details presented on classification of severity of illness). Mean duration of illness was found to be shorter in the amantadine group versus the placebo group ($p < 0.05$).

No evidence relating to health-related quality of life or mortality could be identified for oseltamivir, zanamivir or amantadine.

Adverse events

The measurement and reporting of adverse events varied considerably between included trials and precluded the use of meta-analysis. No strong evidence for a higher incidence of adverse events in treatment groups than in control groups was identified for oseltamivir, zanamivir or amantadine. Few serious drug-related adverse events and drug-related withdrawals were reported.

The study by Peters *et al.* (2001)[61] demonstrated a slightly higher incidence of headaches (8.3% vs. 5.5%) and gastrointestinal (GI) adverse events (14.9% vs. 12.9%) (statistical significance not reported) in frail, elderly individuals receiving oseltamivir than among placebo group subjects. Two studies reported that GI adverse effects were marginally higher amongst the oseltamivir-treated subjects, with GI adverse events being reported in 9.3% and 7.2% of oseltamivir and placebo group subjects respectively[59] and a higher proportion of subjects in the oseltamivir arm experiencing upper GI adverse events (specifically nausea) (12.1% vs. 7.1%, a difference of 5.0%, 95% CI 1.4—8.6) and vomiting (2.5% vs. 0.8%, a difference of 1.7%, 95% CI 0.2—3.3).[62] Adverse events were similar in both treatment arms and across all studies of zanamivir prophylaxis. Withdrawals due to adverse events and illness were similar in amantadine and placebo groups, whilst adverse effects were similar in both groups, with the exception of limited data from the trial reported by Smorodintsev *et al.*[68, 69] from a subset of non-ill subjects ($n = 1825$) questioned from the amantadine and treatment groups, which indicated a non-significant 2.1% excess in adverse events in the amantadine group (7.2%, 94/1313) vs placebo group (5.1%, 26/512), with statistically significant ($p < 0.05$) excesses in dyspepsia (1.72%) and sleep disturbances (1.14%).

Vaccination status

Details of the vaccination status of study populations are presented in Tables 1–3 where available. The protective efficacy of oseltamivir in elderly subjects in seasonal prophylaxis when analysed among vaccinated subjects only was found to be comparable with the protective efficacy among the study population as a whole (protective efficacies of 91% and 92% respectively).[61]

The use of zanamivir in seasonal prophylaxis in healthy adults aged 18–64 years yielded a 68% (calculated by assessment group) protective efficacy against SLCI (95% CI 37%, 83%).[72] Among unvaccinated subjects, the protective efficacy appeared to be marginally lower at 60% (95% CI 24%–80%). For the use of zanamivir in seasonal prophylaxis in at-risk adults and adolescents, comparable effects were observed, with relative risks of 0.17 (95% CI 0.02–1.41) and 0.17 (95% CI 0.05–0.58) of developing SLCI in vaccinated and unvaccinated subjects respectively.[73] Of the cases of SLCI that were observed in a trial[66] of zanamivir in outbreak control all occurred in unvaccinated subjects.

Limited evidence was identified relating to the impact of vaccination status on the efficacy of amantadine prophylaxis. The study by Payler and Purdham[67] (in which the study population was 87% vaccinated) demonstrated that, of the three subjects developing SLCI in the amantadine-treated arm, two were vaccinated whilst one subject was reported as unvaccinated. No information was given for the control arm.

Antiviral resistance

No evidence of reduced sensitivity of tested viral isolates to oseltamivir or zanamivir was obtained in included studies. None of the amantadine prophylaxis trials included in this review reported the assessment of sensitivity of influenza isolates to amantadine.

Discussion

Oseltamivir was demonstrated to prevent SLCI in seasonal prophylaxis in healthy adults and at-risk elderly subjects and in post-exposure prophylaxis within households of mixed composition. Post-exposure prophylaxis using oseltamivir for paediatric contacts was also shown to be effective in preventing influenza. Evidence relating to the efficacy of zanamivir in preventing SLCI was observed in trials of seasonal prophylaxis in healthy adults, at-risk adults and adolescents, and in post-exposure prophylaxis in households of mixed composition, with a trend for seasonal and post-exposure preventative effects among elderly subjects. Whilst the evidence for amantadine prophylaxis across subgroups was very limited, the effectiveness of amantadine in preventing SLCI in seasonal prophylaxis in healthy adults and in outbreak control amongst adolescent subjects was reported.

Very limited data were identified relating to the benefits of the interventions in preventing complications and hospitalisations and in minimising length of illness and return to normal activities. No data could be identified concerning health-related quality of life or mortality outcomes.

No trials were identified to evaluate the efficacy of amantadine in seasonal prophylaxis in at-risk adults and adolescents, post-exposure prophylaxis in households of mixed composition, or post-exposure prophylaxis in at-risk adults and adolescents or elderly subjects. No evidence was found relating to the use of oseltamivir in seasonal prophylaxis in at-risk adults and adolescents, seasonal prophylaxis in healthy elderly subjects, or post-exposure prophylaxis in elderly subjects. Furthermore, no trials were available for the evaluation of zanamivir in seasonal or post-exposure prophylaxis in children, post-exposure prophylaxis in adults and adolescents, or healthy elderly subjects.

Strengths and limitations of review

The scope of this review was comprehensive, covering the use of three antiviral interventions in two prophylactic strategies across a broad range of population subgroups. The methods used for reviewing the evidence were comprehensive and rigorous. However, a limitation of the review relates to the limiting of included studies by language. Searches were not restricted by language, but studies other than those published in the English language were excluded. Seven citations were excluded as the full text was not available in English.[13–19] It should also be noted that none of the included studies investigated the efficacy of antiviral prophylaxis against pandemic strains of influenza.

Comparison with related literature

Our review provides an update of the previous assessment of the use of oseltamivir and zanamivir in the prevention of influenza reported by Cooper *et al*. (2003).[77] Whilst our review includes additional evidence published subsequent to the searches conducted by Cooper *et al*. (search end date of December 2001), our conclusions are similar in that, whilst oseltamivir and zanamivir appear to be effective in the prevention of influenza, evidence is lacking for some patient populations and prophylactic strategies. Our review also included all of the trials of the efficacy of neuraminidase inhibitors in the prevention of influenza that were described in the systematic review of the effects of neuraminidase inhibitors as prophylaxis in children reported by Shun-Shin *et al*. (2009)[78] (NAI30010; NAI30031; WV16193) and our findings support their conclusion that post-exposure prophylaxis with neuraminidase inhibitors may reduce the risk of developing SLCI among paediatric subjects. Jefferson *et al*. [79] conducted a systematic review of neuraminidase inhibitors in the prevention of influenza in healthy adults. Our review contained the same prophylaxis studies as the Jefferson review, with the exception of the report by Kashiwagi *et al*. (2000),[17] which was not available in full in English and was therefore excluded from this review. Our review concurs with their conclusion that current evidence indicates that neuraminidase inhibitors are effective in post-exposure prophylaxis against SLCI but that further research is required to address evidence gaps.

Implications for practice

A number of issues relating to the external validity of the included studies should be taken into consideration during interpretation of the evidence base. Subjects who were unable to understand study personnel were excluded from trial participation in the zanamivir trials reported by Ambroizaitis *et al*. and Gravenstein *et al*. Peters *et al*. and Welliver *et al*. excluded individuals scoring below 7 on a mental status questionnaire from study participation.

None of the amantadine prophylaxis trials included in this review reported the assessment of sensitivity of influenza isolates to amantadine. However, the development of amantadine-resistant influenza A strains presents a significant challenge to the use of amantadine in prophylaxis against influenza and must be taken into consideration. No evidence of reduced sensitivity of viral isolates to oseltamivir or zanamivir was obtained in the studies included in this review. However, Health Protection Agency surveillance data[80] from within the UK indicated variable levels of resistance to antivirals. In the 2008 to 2009 season, of 91 influenza A (H1N1) isolates tested, 90 (99%) were resistant to oseltamivir but retained sensitivity to zanamivir and amantadine. For the same period, all of 231 influenza A (H3) isolates were resistant to amantadine, but not oseltamivir or zanamivir. Similarly, of 44 influenza B isolates tested, none were resistant to oseltamivir or zanamivir. The evidence for the use of antivirals in prophylaxis against influenza should therefore be interpreted in light of the potential for emerging resistance. The potential generation of antiviral resistance as a result of the use of the interventions during the H1N1 pandemic that began in 2009 should also be carefully monitored. As of July 2010, the WHO stated that a cumulative total of 298 cases of oseltamivir-resistant pandemic influenza A (H1N1) 2009 viruses had been reported, all but one of which had the H275Y substitution and were assumed to retain sensitivity to zanamivir.[81]

It should also be noted that antivirals were administered to study participants within the appropriate timeframe stated in the licensed indications for each intervention and, therefore, timely patient presentation and prescription of antivirals would be integral to effective prophylaxis in clinical practice.

Areas for future research

Whilst a considerable amount of evidence was identified relating to the use of antiviral prophylaxis of influenza, a number of areas warrant further research. Further studies among those population groups considered at higher risk of influenza-associated complications are necessary to strengthen the evidence base for efficacy in the most clinically relevant subgroups. There is a particular requirement for further evidence relating to the clinical effectiveness of antivirals in post-exposure prophylaxis amongst elderly subjects, particularly in long-term care settings, since subjects over 65 years of age were not well represented within the post-exposure prophylaxis trials. Further evidence gaps (see Tables 4 and 5) were also noted in which further studies may be of value. Studies of influenza antiviral prophylaxis in which the effect of the confounding variable of vaccination is further explored are recommended.

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