Antivirals for influenza in healthy adults: systematic review

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Summary

Background Use of antivirals is recommended for the control of seasonal and pandemic influenza. Our aim was to review the evidence of efficacy, effectiveness, and safety of registered antivirals against naturally occurring influenza in healthy adults.

Methods We searched various Databases to October, 2005, and contacted manufacturers and corresponding authors. We included randomised controlled trials comparing prophylactic (n=27) or treatment (n=27) efficacy against symptomatic or asymptomatic influenza. We did a meta-analysis and expressed prophylactic efficacy as a proportion (1–relative risk [RR]). For treatment trials, because of inconsistent and non-standardised reporting, we expressed continuous outcomes either as means or as hazard ratios.

Findings We included 51 reports of 52 randomised controlled trials. Amantadine prevented 61% (95% CI 35–76) of influenza A cases and 25% (13–36) of cases of influenza-like illness, but caused nausea (OR 2·56, 1·37–4·79), insomnia and hallucinations (2·54, 1·50–4·31), and withdrawals because of adverse events (2·54, 1·60–4·06). There was no effect on asymptomatic cases (RR 0·85, 0·40–1·80). In treatment, amantadine significantly shortened duration of fever compared with placebo (by 0·99 days, −1·26 to −0·71), but had no effect on nasal shedding of influenza A viruses (0·93, 0·71–1·21). The fewer data for rimantadine showed comparable effects. In prophylaxis, compared with placebo, neuraminidase inhibitors have no effect against influenza-like illness (1·28, 0·45–3·66 for oral oseltamivir 75 mg daily, 1·51, 0·77–2·95 for inhaled zanamivir 10 mg daily). Higher doses appear to make no difference. The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza is 61% (15–82), or 73% (33–89) at 150 mg daily. Inhaled zanamivir 10 mg daily is 62% efficacious (15–83). Neither neuraminidase inhibitor appeared effective against asymptomatic influenza. Oseltamivir induces nausea (OR 1·79, 1·10–2·93), especially at higher prophylactic doses (2·29, 1·34–3·92). Oseltamivir in a post-exposure prophylaxis role has a protective efficacy of 58·5% (15·6–79·6) for households and from 68% (34·9–84·2) to 89% (67–97) in contacts of index cases. In influenza cases, compared with placebo the hazard ratios for time to alleviation of symptoms were 1·33, 1·29–1·37 for zanamivir; 1·30, 1·13–1·50 for oseltamivir provided medication was started within 48 h of symptom onset. Viral nasal titres were significantly diminished by both drugs (weighted mean difference –0·62, –0·82 to –0·41). Oseltamivir at 150 mg daily was effective in preventing lower respiratory tract complications in influenza cases (OR 0·32, 0·18–0·57). We could find no credible data on the effects of oseltamivir on avian influenza.

Interpretation The use of amantadine and rimantadine should be discouraged. Because of their low effectiveness, neuraminidase inhibitors should not be used in seasonal influenza control and should only be used in a serious epidemic or pandemic alongside other public-health measures.

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Introduction

The M2 ion channel-blocking drugs amantadine and rimantadine and the newer generation, more expensive antiviral compounds (neuraminidase inhibitors) nebulised zanamivir (Relenza, Glaxo Wellcome, NC, USA) and oral oseltamivir (Tamiflu, Gilead Sciences, CA, USA, and Hoffman La Roche, Basel, Switzerland) have anti-influenza activity.[1,2] In 2005, WHO encouraged member countries to use antivirals in influenza interpandemic periods because "wide scale use of antivirals and vaccines during a pandemic will depend on familiarity with their effective application during the interpandemic period. The increasing use of these modalities will expand capacity and mitigate the morbidity and mortality of annual influenza epidemics".[3] The European Medicines Agency maintains that neuraminidase inhibitors (especially oseltamivir) are complementary to vaccines, and should be used in an influenza pandemic[4] for treatment of index cases and for influenza prophylaxis in key personnel—namely, police officers, fire fighters, health-care workers. None of the systematic reviews done[5–7] of the effects of antivirals, however, is up to date, and none has assessed their potential role in an influenza pandemic, where high viral load and high transmission seem to be the norm. In this context, trade-off between dose and adverse-event profile in prophylaxis, activity against influenza infection in those with and without symptoms, and extent of viral excretion through body fluids become important.[2] Cost is also likely to be a factor when choosing a drug for use in epidemic or pandemic situations.

Our aim, was to assess the comparative studies of the efficacy (against laboratory-confirmed influenza with or without symptoms), effectiveness (against influenza-like illness), and safety of antivirals against influenza in healthy adults. This report is based on two Cochrane reviews,[8,9] which we are in the process of updating.

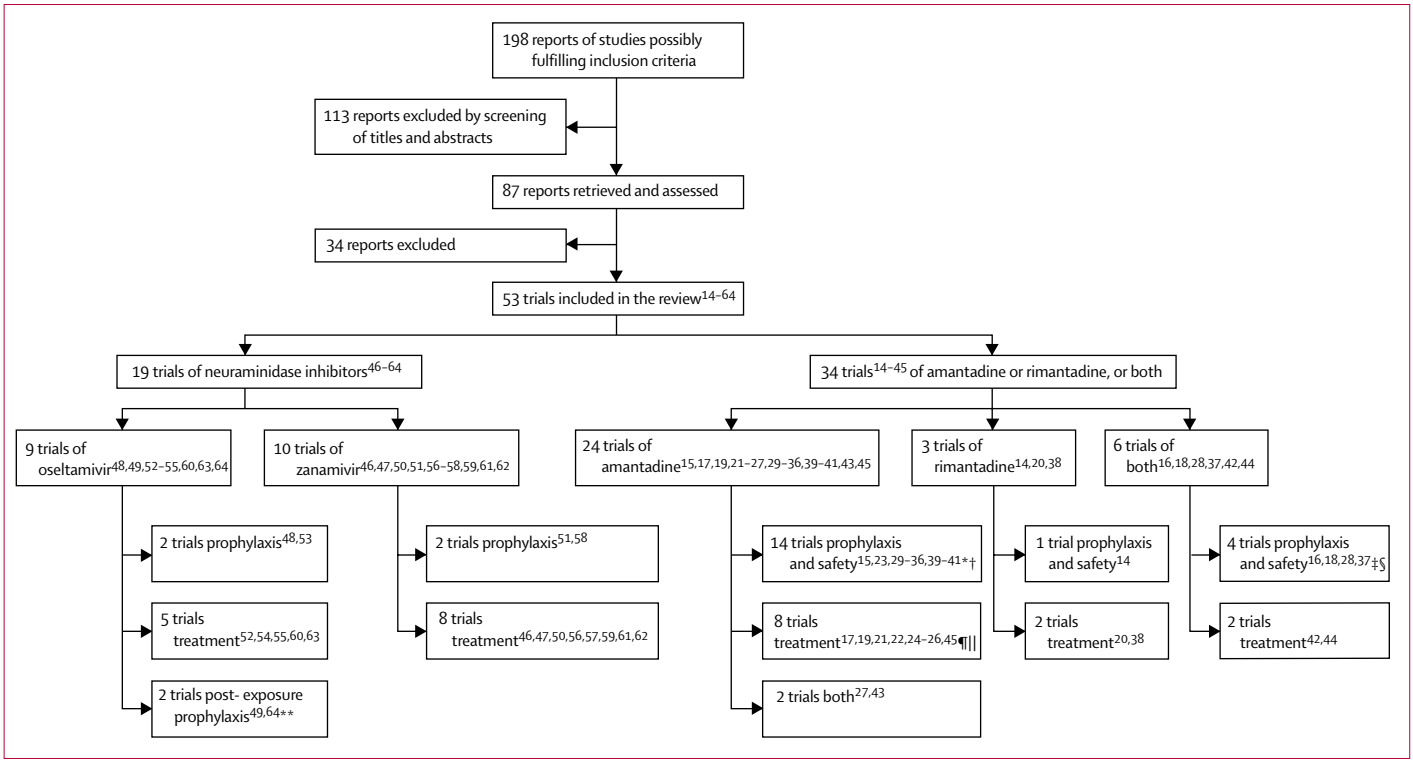

Figure: **Trials included**

*One trial[33] had no intervention in control group. †One report[34] contained data for three trials, two of which had sufficient outcome data. ‡Two trials[23,45] had symptomatic medication as a comparator. §One trial[28] had symptomatic medication as a comparator. ¶One trial[21] broken down further into four subtrials in different locations. ||Two trials[18,28] considered adverse effects only. **One of these two trials[49] was an open cluster randomised controlled trial, all others were placebo controlled randomised controlled trials.

Methods

See Online for webappendix

Search strategy (webappendix) and selection criteria

We searched Ovid MEDLINE (to August, 2005), WebSpirs EMBASE (to June, 2005), and the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2005), and checked the references of systematic reviews of the topic[5–7] and of retrieved trials, for relevant published work. We wrote to manufacturers and authors of identified studies for further information.

We considered for inclusion in our systematic review randomised controlled trials that assessed the prophylactic or treatment effects of amantadine, rimantadine, and neuraminidase inhibitors compared with placebo, no intervention, or symptomatic medication in any dose, preparation, or time schedule in people in any geographical location who were otherwise healthy and aged 16–65 years. We also considered evidence of the effects on transmission of seasonal and avian influenza.

We considered the following outcome measures: cases of symptomatic or asymptomatic influenza confirmed by means of viral isolation or by serological or any other type of laboratory testing for viral identification (influenza cases); cases of influenza-like illness (influenza symptoms without laboratory confirmation); cases of pneumonia; cases of influenza or influenza-like illness admitted to hospital for treatment of complications; deaths (due to influenza or influenza-like illness); duration and concentration of nasal shedding of viruses or persistence in the upper airways; and cases of human influenza caused by avian-derived influenza viruses.

Data extraction and study validity assessment

Two reviewers (TJ and VD) independently applied inclusion criteria to all identified and retrieved articles. Two reviewers (TJ and DR) extracted data from included studies on standard forms. This procedure was supervised and arbitrated by VD. We assessed the methodological quality of randomised controlled trials, using criteria from the *Cochrane Reviewers' Handbook*.[10] We assessed studies according to their randomisation schedule, generation of the allocation sequence, allocation concealment, blinding, and follow up. We entered extracted data into Cochrane RevMan software (version 1.0). Aggregation of data was dependent on the sensitivity and consistency of definitions of exposure, populations, and outcomes used.

We used the inverse variance method to weight each study. For random effects meta-analysis, we used the DerSimonian and Laird method.[10] We estimated the

	Outcome	Datasets	Observations	Results (95% CIs)
Prophylaxis				
Oral amantadine *vs* placebo	Influenza-like illness cases	15[15,16,29,31–37,40,41,43]	17 496	Effectiveness 25% (13 to 36)*
	Influenza cases	11[16,23,27,29–33,35,37,39]	4645	Efficacy 61% (35 to 76)*
	Influenza cases (asymptomatic)	4[14,16,29,31]	963	RR 0·85 (0·40 to 1·80)
	Viral shedding	1[39]	79	Efficacy 32% (13 to 47)*
Oral rimantadine *vs* placebo	Influenza-like illness cases	3[14,16,37]	688	RR 0·65 (0·35 to 1·20)
	Influenza cases	3[14,16,37]	688	RR 0·28 (0·08 to 1·08)
	Influenza cases (asymptomatic)	1[16]	265	RR 1·39 (0·45 to 4·27)
Oral amantadine *vs* oral rimantadine	Influenza-like illness cases	2[16,37]	455	RR 0·88 (0·57 to 1·35)
	Influenza cases	2[16,37]	455	RR 0·89 (0·48 to 1·65)
Treatment				
Oral amantadine *vs* placebo	Duration of fever (days)	10[17,21,24–27,44]	542	WMD −0·99 (−1·26 to −0·71)*
	Duration of hospital stay (days)	1[27]	36	WMD −0·90 (−2·20 to 0·40)
	Cases with fever at 48 h	2[42,44]	85	Efficacy 79% (34 to 93)*
	Viral shedding at 5 days	3[21,42,44]	170	RR 0·96 (0·72 to 1·27)
Oral rimantadine *vs* placebo	Duration of fever (days)	3[20,38,44]	82	WMD −1·24 (−1·71 to −0·76)*
	Cases with fever at 48 h	4[20,38,42,44]	122	Efficacy 84% (47 to 95)*
	Viral shedding at 5 days	3[20,42,44]	152	RR 0·67 (0·22 to 2·07)
Oral amantadine *vs* oral rimantadine	Duration of fever (days)	1[44]	40	WMD 0·20 (−0·56 to 0·96)
	Cases with fever at 48 h	2[42,44]	73	RR 0·99 (0·23 to 4·37)
Oral amantadine *vs* standard medication care	Duration of fever (days)	2[22,45]	78	WMD 0·25 (−0·37 to 0·87)
	Viral shedding at 5 days	1[45]	47	RR 0·71 (0·44 to 1·13)
Oral or inhaled amantadine *vs* placebo or aspirin	Viral shedding at 5 days	5[19,21,42,44,45]	237	RR 0·93 (0·71 to 1·21)

*Significant at $p<0·05$. WMD=weighted mean difference.

Table 1: **Efficacy and effectiveness of amantadine and rimantadine**

proportion of total variation in the study estimates due to heterogeneity with the I^2 statistic.[11]

We undertook a sensitivity analysis by seasonal or pandemic influenza, comparing our results obtained with the fixed effects and random effects models. In the prophylaxis trials, efficacy was derived as 1–RR (relative risk)×100 (where not significant, we report the RR). We used odds ratios to estimate the association of adverse effects with exposure to antivirals. In treatment trials, our choice of methods for combining the estimates of severity of influenza depended on the format in which the data were presented.[11] For amantadine and rimantadine, we compared the mean duration of symptoms in the two groups and express differences as weighted mean difference. When the data were presented as the number of patients with duration of symptoms beyond a cut-off time, we present data as cases with fever at 48 h. We analysed the effects on cases, stratified either as influenza (a defined set of signs and symptoms confirmed by serology or isolation of influenza virus from nasal fluids, or both) or clinical criteria alone (influenza-like illness) or asymptomatic cases (serological confirmation or isolation of influenza virus from nasal fluids of people without symptoms, or both). We considered meta-analysing symptom outcome data to further inform the assessment of the effects of amantadine or rimantadine in the treatment role, but outcome typology was too diverse to allow aggregation. We resorted to using duration of fever (a temperature higher than 37°C) as the only common outcome. In the treatment trials of neuraminidase inhibitors, analysis of time to alleviation of symptoms outcome and time to return to normal activity outcome provided some difficulty because of their inconsistent and non-standard reporting across trials. Most reports described these outcomes in terms of medians for each treatment group. However, standard reporting in a meta-analysis requires these outcomes to be expressed as (log) hazard ratios. If it is assumed that the treatment effect is constant over time (as seems reasonable), then the ratio of the medians can be used to estimate the hazard ratio. To estimate the variance of the log hazard ratio, we used the method described by Parmar, Torri, and Stewart.[12] We estimated the number of events from survival curves when these were available or, when they were not available, assumed that all patients completed the trial, providing follow up was long enough for this assumption to be a reasonable one. We converted data with respect to nasal viral titre for two studies into means and standard deviations (SDs) to be consistent with other studies and allow meta-analysis. We converted means directly from the medians, since both are measures of central tendency and should be similar for approximately symmetrical data. We converted the range to an SD, using the method described by Hurlburt.[13] The interquartile range (IQR) was converted to SD by multiplying by 68/50 (since 50% of the data are contained within the IQR, while ±1 SD contains 68% of the data, providing it is approximately normally distributed) then dividing by 2 (to estimate 1 SD). We assessed the effect of this conversion with a sensitivity analysis by excluding data from the two studies and comparing the results.

	Outcome	Datasets	Observations	Results (95% CIs)
Prophylaxis				
Oral amantadine *vs* placebo	Gastrointestinal	5[15,18,36,39,41]	3336	OR 2·56 (1·37 to 4·79)*
	Increased CNS activity	9[15,16,18,29,32,36,39,41,43]	5002	OR 2·54 (1·50 to 4·31)*
	Decreased CNS activity	7[15,28,29,32,36,39,41]	3797	OR 1·73 (0·86 to 3·45)
	Dermatological changes	3[15,29,33]	918	OR 1·55 (0·39 to 6·20)
	All adverse effects	6[18,35–37,39,41]	4274	OR 1·70 (0·99 to 2·93)
	Withdrawals due to adverse effects	6[16,18,29,35,36,37]	2276	OR 2·54 (1·60 to 4·06)*
Oral rimantadine *vs* placebo	Gastrointestinal	2[14,18]	257	OR 4·39 (1·43 to 13·52)*
	Increased CNS activity	3[14,16,18]	652	OR 1·58 (0·78 to 3·19)
	Decreased CNS activity	2[14,28]	243	OR 1·31 (0·23 to 7·50)
	All adverse effects	3[14,18,37]	558	OR 1·96 (1·19 to 3·22)*
	Withdrawals due to adverse effects	3[16,18,37]	625	OR 1·10 (0·48 to 2·51)
Oral amantadine *vs* oral rimantadine	Gastrointestinal	1[18]	130	OR 1·28 (0·51 to 3·16)
	Increased CNS activity	2[16,18]	232	OR 3·11 (1·67 to 5·78)*
	All adverse effects	2[18,37]	339	OR 1·60 (0·28 to 9·26)
	Withdrawals due to adverse effects	3[18,37]	631	OR 2·49 (1·26 to 4·93)*
Treatment				
Oral amantadine *vs* placebo	Gastrointestinal	3[24–26]	494	OR 1·34 (0·32 to 5·61)
	Increased CNS activity	2[24,25]	465	OR 0·77 (0·23 to 2·53)
	Decreased CNS activity	3[24–26]	491	OR 0·65 (0·31 to 1·38)
	Dermatological changes	2[24,25]	465	OR 1·40 (0·14 to 13·78)
Oral rimantadine *vs* placebo	Increased CNS activity	1[20]	14	OR 1·00 (0·10 to 10·17)
	Decreased CNS activity	1[42]	31	OR 0·20 (0·01 to 5·24)
Oral amantadine *vs* oral rimantadine	Decreased CNS activity	1[42]	33	OR 22·58 (1·13 to 452·21)*

Decreased CNS activity=depression, fatigue. Increased CNS activity=hallucinations, insomnia, agitation. *Significant at $p<0·05$.

Table 2: Adverse effects of amantadine and rimantadine

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 87 reports of studies possibly fulfilling our inclusion criteria (figure 1).[14–64] We included 20 reports of 21 prophylaxis and safety trials for amantadine and rimantadine and 13 treatment trials. Two trials contained both treatment and prophylaxis data,[27,43] but only one[27] had extractable treatment data. One report[34] contained data for three trials, two of which had sufficient outcome data. One trial[21] was broken down into four subtrials in different locations. Two trials[18,28] considered adverse effects only, and 12 prophylaxis trials and seven treatment trials reported sufficient data on adverse effects. Three trials[22,28,45] had symptomatic medication as a comparator, one had no intervention,[33] and the rest were placebo-controlled. Ten reports related to 11 trials had been done during the 1968–69 pandemic.[17,24,26,27,30–32,34,40,41]

See Online for webtables 1 and 2

We included 19 studies of neuraminidase inhibitors: four prophylaxis trials, two assessing zanamivir and two assessing oseltamivir; and eight treatment trials of zanamivir and five of oseltamivir. Two zanamivir trials[46,47] were publications linked to other studies[59,62] and provided additional data. One oseltamivir study included supplementary outcome data from all treatment trials.[52] We identified two post-exposure prophylaxis trials of different design.[49,64] Although a proportion of the post-exposure prophylaxis studies were done on children, we decided to include them since they provide important evidence on interruption of transmission. All included studies were placebo-controlled randomised controlled trials except the study by Hayden and colleagues,[49] which was an open cluster randomised controlled trial.

We also identified four reports of ad-hoc studies and additional information of the role of oseltamivir in avian influenza.[2,65–68]

See webtable 1 and webtable 2 for a full description of all included trials. The most common reasons for exclusion of studies was their assessment of experimentally-induced influenza or of individuals older than 65 years or younger than 16 years (six studies each, 18% each of total). A list of the 34 excluded studies is available from the corresponding author on request.

Of the 20 prophylaxis trials of amantadine and rimantadine, 17 stated that the allocation method was randomisation, but only four mentioned a particular method,[14,29,35,39] two did not mention random allocation,[36,40] and all claimed to be double blind. One trial was open-label, comparing the effects of amantadine with no intervention.[33] Of the 13 treatment trials, 11 stated that the allocation method was randomisation and no trials mentioned a particular method. One trial[21] did not mention random allocation, and for another[22] very limited information was

	Outcome	Datasets	Observations	Results (95%CI)
Prophylaxis				
Oral oseltamivir 75 mg *vs* placebo	Influenza-like illness cases	2[48,53]	1088	RR 1·28 (0·45 to 3·66)
	Influenza cases	2[48,53]	1087	Efficacy 61% (15 to 82)*
	Influenza cases (asymptomatic)	2[48,53]	1087	RR 0·73 (0·43 to 1·26)
Oral oseltamivir 150 mg *vs* placebo	Influenza-like illness cases	1[48]	779	RR 1·00 (0·25 to 3·95)
	Influenza cases	1[48]	780	Efficacy 73% (33 to 89)*
	Influenza cases (asymptomatic)	1[48]	780	RR 0·67 (0·35 to 1·28)
Inhaled zanamivir 10 mg *vs* placebo	Influenza-like illness cases	2[51,58]	1299	RR 1·51 (0·77 to 2·95)
	Influenza cases	2[51,58]	1299	Efficacy 62% (15 to 83)*
	Influenza cases (asymptomatic)	1[58]	1107	RR 1·63 (0·99 to 2·67)
Intranasal zanamivir 0·32 mg *vs* placebo	Influenza-like illness cases	1[51]	189	RR 0·79 (0·21 to 2·95)
	Influenza cases	1[51]	189	RR 1·06 (0·54 to 2·08)
Inhaled and intranasal zanamivir 10 mg and 0·32 mg *vs* placebo	Influenza-like illness cases	1[51]	194	RR 0·33 (0·07 to 1·58)
	Influenza cases	1[51]	194	Efficacy 78% (42 to 92)*
Neuraminidase inhibitors (all) *vs* placebo	Influenza-like illness cases	7[48,51,53,58]	3549	RR 1·20 (0·77 to 1·87)
	Influenza cases	7[48,51,53,58]	3549	Efficacy 59% (35 to 75)*
	Influenza cases (asymptomatic)	4[48,53,58]	2974	RR 0·93 (0·57 to 1·51)
Treatment				
Oral oseltamivir 75–150 mg *vs* placebo	Time to alleviation of symptoms (ITT)	3[55,60,63]	1797	HR 1·20 (1·06 to 1·35)*
	Time to alleviation of symptoms (influenza cases only)	4[54,55,60,63]	1374	HR 1·30 (1·13 to 1·50)*
	Time to return to normal activity (ITT)	1[63]	627	HR 1·23 (1·02 to 1·48)*
	Time to return to normal activity (influenza cases only)	1[63]	374	HR 1·34 (1·07 to 1·67)*
	Complication—bronchitis (influenza cases only)	1[52]	1644	OR 0·40 (0·21 to 0·76)*
	All lower respiratory tract complications (influenza cases only)	1[52]	1644	OR 0·32 (0·18 to 0·57)*
	Complication—pneumonia (influenza cases only)	1[52]	1644	OR 0·15 (0·03 to 0·69)*
	Complication—all hospitalisations (influenza cases only)	1[52]	1644	OR 0·40 (0·10 to 1·69)
	Complication—hospitalisations from influenza (influenza cases only)	1[52]	1644	OR 0·22 (0·02 to 2·16)
	Complication—all types (influenza cases only)	1[52]	1644	OR 0·30 (0·20 to 0·46)*
	Complication—all types (ITT)	1[52]	2358	OR 0·39 (0·28 to 0·55)*
	Use of relief medications and antibiotics	2[55,60]	992	OR 1·01 (0·67 to 1·52)
	Mean nasal viral titre at 24 h (concentration)	2[60,63]	561	WMD −0·73 (−0·99 to −0·47)*
Inhaled zanamivir *vs* placebo	Time to alleviation of symptoms (ITT)	6[50,56,57,59,61,62]	3188	HR 1·24 (1·13 to 1·36)*
	Time to alleviation of symptoms (influenza cases only)	7[47,50,56,57,59,61,62]	2117	HR 1·33 (1·29 to 1·37)*
	Time to return to normal activity (ITT)	3[57,59,62]	1827	HR 1·28 (1·13 to 1·45)*
	Time to return to normal activity (influenza cases only)	3[50,56,62]	860	HR 1·17 (1·00 to 1·37)
	Complication—all types (influenza cases only)	1[56]	277	OR 0·64 (0·38 to 1·08)
	Complication—all types (ITT)	1[56]	356	OR 0·50 (0·32 to 0·76)*
	Use of relief medications and antibiotics	2[46,57]	838	OR 0·64 (0·41 to 1·01)
	Mean nasal viral titre at 24 h (concentration)	2[47,61]	441	WMD −0·40 (−0·75 to −0·06)*
Neuraminidase inhibitors (all) *vs* placebo	Time to alleviation of symptoms (ITT)	9[50,55–57,59–63]	4985	HR 1·22 (1·14 to 1·31)*
	Time to alleviation of symptoms (influenza cases only)	11[47,50,54–57,59–63]	3491	HR 1·32 (1·26 to 1·38)*
	Time to return to normal activity (ITT)	4[62,57,59,63]	2454	HR 1·26 (1·14 to 1·40)*
	Time to return to normal activity (influenza cases only)	4[62,56,50,63]	1234	HR 1·22 (1·07 to 1·39)*
	Complication—all types (influenza cases only)	2[52,56]	1921	OR 0·43 (0·21 to 0·90)*
	Complication—all types (ITT)	2[52,56]	2714	OR 0·43 (0·33 to 0·56)*
	Use of relief medications and antibiotics	4[46,57,55,60]	1830	OR 0·82 (0·60 to 1·11)
	Mean nasal viral titre at 24 h (concentration)	4[47,61,60,63]	1002	WMD −0·62 (−0·82 to −0·41)*

ITT=intention to treat. WMD=weighted mean difference.*Significant at $p<0·05$.

Table 3: **Efficacy and effectiveness of neuraminidase inhibitors**

available. Major flaws in the reporting of trials were: lack of information on the completeness of follow-up and a detailed description of methods used to conceal allocation, frequent inconsistencies in the reporting of numerators and denominators in various arms of trials, and, in the treatment trials, the use of a bewildering variety of outcomes. For neuraminidase inhibitors, one prophylaxis trial had adequate methodological quality,[58] one had unclear measures to protect double blinding,[48] and two[51,53] had poorly described methods. One study[51] reported no dropouts. Four treatment studies[56,60,62,63] were of adequate methodological quality and four[46,47,52,54] had unclearly described procedures, although three[52,46,47] were linked to larger studies. The remainder had at least one unclearly described item. One trial[55] did not include withdrawals in the analysis.

Withdrawals were included in both post-exposure prophylaxis trials, but all other items were poorly described.

Amantadine and rimantadine: treatment and prophylaxis

Table 1 and table 2 show our results for the use of amantadine and rimantadine for treatment and prophylaxis. In our prophylaxis analysis, amantadine prevented 61% of influenza A cases and 25% of cases of

	Outcome	Datasets	Observations	Results (95%CI)
Prophylaxis				
Oral oseltamivir 75 mg *vs* placebo	Nausea	2[48,53]	1088	OR 1·79 (1·10–2·93)*
	Vomiting	2[48,53]	1088	OR 2·28 (0·87–5·95)
	Diarrhoea	1[53]	308	OR 0·58 (0·28–1·20)
	Abdominal pain	1[53]	308	OR 0·99 (0·49–1·97)
	Others	1[53]	308	OR 0·95 (0·59–1·55)
	Withdrawals due to gastrointestinal events	1[48]	779	OR 3·51 (0·18–68·21)
Oral oseltamivir 150 mg *vs* placebo	Nausea	1[48]	779	OR 2·29 (1·34–3·92)*
	Vomiting	1[48]	779	OR 3·57 (0·81–15·82)
	Withdrawals due to gastrointestinal events	1[48]	780	OR 3·52 (0·18–68·47)
Treatment				
Oral oseltamivir 150 mg *vs* placebo	Cough	1[55]	273	OR 1·31 (0·53–3·22)
	Headache	1[55]	273	OR 0·96 (0·45–2·05)
	Diarrhoea	1[54]	313	OR 0·56 (0·28–1·13)
	Nasal symptoms (congestion, rhinitis, dry, sore throat)	1[55]	273	OR 0·85 (0·51–1·44)
	Nausea	2[54,63]	928	OR 1·80 (0·73–4·41)
	All types	1[54]	313	OR 0·67 (0·43–1·05)
Inhaled zanamivir *vs* placebo	Cough	2[61,62]	1043	OR 1·40 (0·14–13·49)
	Headache	2[57,59]	1352	OR 0·87 (0·39–1·97)
	Diarrhoea	4[57,59,61,62]	2415	OR 0·78 (0·37–1·63)
	Nasal symptoms (congestion, rhinitis, dry, sore throat)	3[59,61,62]	2299	OR 0·98 (0·47–2·06)
	Nausea	3[56,59,62]	2067	OR 0·63 (0·36–1·10)
	Bronchitis or pneumonia	3[59,61,62]	2299	OR 0·73 (0·24–2·26)
	All types	3[57,61,62]	1159	OR 0·88 (0·69–1·14)

*Significant at $p<0·05$.

Table 4: Adverse effects of neuraminidase inhibitors

influenza-like illness. Both of these results are significant (table 1). There was no effect on asymptomatic cases, nor any difference in efficacy between unvaccinated (RR 0·45, 0·28–0·74) and vaccinated (RR 0·10, 0·03–0·34) individuals. The effectiveness of amantadine in unvaccinated individuals was significantly higher (25%, 10–38) than that of placebo, but not in vaccinated individuals (0·42, 0·07–2·52). Gastrointestinal symptoms (mainly nausea), insomnia and hallucinations, and withdrawals from the trials because of adverse events were significantly more common in participants who received amantadine than placebo (table 2). Results of an analysis with a fixed effects model show a significant association with depression, insomnia, and the all adverse events category.

When possible we stratified comparisons on the basis of whether participants had received vaccination or not. Rimantadine was not effective prophylaxis against either influenza or influenza-like illness (table 1); however, analysis with a fixed effects model showed protection against influenza and influenza-like illness in unvaccinated participants. Although these results are not conventionally significant (p=0·07 and p=0·17, respectively), the estimates are based on 688 individuals, and are of a very similar magnitude to those for amantadine. Based on one study[16] only there was no effect on asymptomatic cases (table 1). Recipients of rimantadine were also more likely to experience adverse effects than placebo recipients. However, there was no evidence of an increase in central nervous system (CNS)-related effects and withdrawal rates were similar in both groups (table 2).

We noted no evidence of a difference in efficacy between amantadine and rimantadine, although the confidence interval is quite wide (table 1). CNS adverse effects and withdrawal from trials were significantly more frequent in individuals who received amantadine than in those given rimantadine (table 2).

The effects on nasal viral shedding were assessed by a single study for each antiviral.[16,39] In a treatment role, amantadine significantly shortened duration of fever compared with placebo (table 1). Where time to fever clearance data were not available,[42,44] we used a dichotomous outcome (cases with fever at 48 h). The results of this comparison showed that amantadine was significantly better than placebo (RR 0·21, 0·07–0·66). Rimantadine also shortened duration of fever compared with placebo. However, there was no effect with either drug on nasal shedding or persistence of influenza A viruses in the upper airways after up to 5 days of treatment (table 1). It is noteworthy, though, that for rimantadine, this finding might be the result of the small number of observations in this comparison and is sensitive to analysis with a fixed effects model. The sparse data directly comparing amantadine and rimantadine for treatment showed that the efficacy of the two drugs was comparable, although the confidence intervals are very wide (table 1).

There was no evidence that individuals who received amantadine had increased rates of adverse effects compared with those given placebo, but data were only available from three trials[24,25,42] (n=491) and the association with decreased CNS activity is sensitive to the application of a fixed effect model. There were very

few data available for the assessment of adverse effects of rimantadine for treatment (table 2).[20,42]

Oral or inhaled amantadine had no effect on shedding of influenza A viruses after 5 days of treatment despite meta-analysis of five studies with a combined denominator of 237 observations (table 1).

Standard medications (aspirin and other antipyretic or anti-inflammatory drugs or antibiotics) were as effective as amantadine in reducing the length of fever,[45,22] but they do not inhibit viral replication and as such remain a symptomatic remedy.

No trial tested the role of the compounds on workplace outbreak control despite the trial settings (prisons, factories, schools, barracks). In all trials, administration of the compounds commenced when real-time surveillance data indicated circulation of influenza A virus in the community. Treatment started within 48 h of development of symptoms. No trials assessed onset of resistance, but data in one study indicate that 10–27% of patients treated with amantadine secreted drug-resistant virus within 4–5 days of commencing treatment.[1] We did not do subanalysis by dose (100 mg, 200 mg, 300 mg, daily), because of the small size of the resulting meta-analysis.

Separate analysis of the 11 trials done during the 1968–69 pandemic did not affect our findings.

Neuraminidase inhibitors: treatment and prophylaxis

Table 3 and table 4 show our results for the use of neuraminidase inhibitors for treatment and prophylaxis. In a prophylaxis role, compared with placebo, neuraminidase inhibitors have no effect against influenza-like disease. Oseltamivir 75 mg and 150 mg daily appears effective against symptomatic influenza. Inhaled zanamivir 10 mg daily also seems effective. The addition of an intranasal dose does not seem to significantly enhance its prophylactic activity, although this last observation is based on a single study.[51] Oseltamivir 75 mg daily confers 54% protection against symptomatic and asymptomatic influenza (95% CI 32–69). Based on a single study,[48] an increase to 150 mg daily does not appear to enhance its activity (52%, 20–79). Similarly zanamivir has a 43% protective effect (99–50) and, based on a single study,[51] the addition of an intranasal dose does not appear to enhance its activity (RR 0·77, 0·38–1·56). Neither drug has a significant effect on asymptomatic influenza (table 3). These observations are based on three studies (n=2974)[48,58,53] in the presence of relatively high viral circulation (5% in the combined placebo groups). Oseltamivir induces nausea, especially at the higher prophylactic dose (table 4).

Hayden and colleagues[49] report that post-exposure prophylaxis provided an efficacy of 58·5% (15·6–79·6) for households and of 68% (34·9–84·2) for individual contacts. Since there was viral circulation during the study period (184 of 298 index cases had influenza, 66% of which had influenza A/H1N1 and the remainder influenza B virus), effectiveness was high (62·7%, 26–81). Welliver and co-workers[64] report 89% (67–97) protective efficacy in contacts of index cases with influenza and 84% (45–95) for index cases. Neither trial reported the onset of viral resistance after 5[49] and 7 days[64] of prophylaxis at a dose of 75 mg twice daily[49] and once daily.[64] Neither the background rate of infection in the community nor the viral strains are reported, although influenza A and B were co-circulating at the time.

Time to alleviation of symptoms for all enrolled participants irrespective of influenza infection diagnosis was assessed in nine treatment trials.[50,55–57,59–63] The estimated hazard ratios for zanamivir were greater than one, hence in favour of the treated group, and there was no evidence of heterogeneity (I^2=0%). The treated group are 24% more likely to have their symptoms alleviated than the placebo group by a given timepoint (1·24, 1·13–1·36); a similar result was found for oseltamivir. For time to alleviation of symptoms in influenza-positive participants, the hazard ratios were significantly in favour of the treated group (table 3). There was no evidence of heterogeneity for the zanamivir data meta-analysis, but I^2 was 37·5% for oseltamivir. Application of the fixed effects model did not materially alter the hazard ratio.[47,50,54,55–57,59–63]

Time to return to normal activities was assessed by four studies.[57,59,62,63] For all enrolled participants the pooled estimated hazard ratio for zanamivir was significant, as was that for the single study assessing oseltamivir.[63] In influenza-positive participants, the pooled hazard ratio was just below significance for zanamivir[50,56,62] and significant for oseltamivir, although this observation was based on a single study.[63]

Five studies reported assessing the effect of administration of neuraminidase inhibitors on viral load (as estimated by mean nasal titres of excreted viruses at 24 h and 48 h after randomisation).[47,54,60,61,63] Titres were significantly diminished by both zanamivir and oseltamivir (weighted mean difference −0·62, −0·82 to −0·41). The effect is more marked the longer the time since randomisation (and commencement of treatment; data not shown). Exclusion of data from the Treanor[63] and Nicholson[60] studies does not affect our conclusions (see sensitivity analysis described in Methods). Treatment did not, however, suppress viral excretion, irrespective of dose. There were insufficient data to comment on the effects on nasal excretion of viruses of higher doses of medication.

Oseltamivir 150 mg daily is effective in preventing lower respiratory tract complications in influenza cases, especially bronchitis and pneumonia, but not in cases of influenza-like illness (OR 0·21, 95% CI 0·02–2·04). Both neuraminidase inhibitors are effective in preventing all types of complications in the intention-to-treat population (0·49, 0·38–0·62); although these

observations are based on single studies[52,56] the combined denominator is substantial (n=2991).

Neuraminidase inhibitors are not associated with any adverse events when used as treatments as opposed to prophylaxis, although this finding could be the result of the difficulty of separating adverse events from the symptoms of influenza and to the relatively small denominators in the analysis (table 4). Finally, consumption of relief medications and antibiotics is unaffected by use of neuraminidase inhibitors (0·81, 0·59–1·12).

Discussion

The evidence does not support the use of M2 ion channel inhibitors for influenza. Furthermore, it suggests that neuraminidase inhibitors should not be used routinely for seasonal influenza and only with associated public-health measures in a pandemic situation.

As for all systematic reviews, our findings and interpretation are limited by the quantity and quality of available evidence on the effects of a specific intervention for a disease (influenza) or syndrome (influenza-like illness). Because sometimes such evidence is contradictory, we present facts and possible alternative explanations of the facts. Our review identified datasets on two classes of antivirals clearly separated by 30 years worth of improvement in trial conduct and reporting, by our knowledge of influenza and its effects, and by the rationale for the undertaking of clinical trials. Despite these evolutionary differences in knowledge the study design included in our review was the same (randomised controlled trial) and the results are presented separately by intervention and comparison.

Our findings indicate that M2 ion channel-blocking drugs (amantadine and rimantadine) have a mainly symptomatic effect on influenza A, since they do not prevent infection and do not affect viral shedding. Additionally, the possibility of serious adverse effects and swift onset of antiviral resistance[1,69] should discourage their use in seasonal and pandemic influenza, especially if used in isolation from other measures.

Trials of neuraminidase inhibitors were clearly designed and undertaken within a registration and regulation perspective. This fact is reflected in the cryptic reporting of continuous outcome data, which forced us to resort to summary measures such as hazard ratios, which although methodologically virtuous might not be relevant to workers in the field. This group of drugs affects influenza symptoms, either preventing their appearance or curtailing their duration and, although we identified clear evidence of their ability to interrupt transmission of seasonal influenza in households, neuraminidase inhibitors do not appear to prevent asymptomatic infection and decrease but do not interrupt nasal shedding of seasonal influenza viruses. We cannot explain how neuraminidase inhibitors can affect respiratory complications of seasonal influenza, such as bronchitis and pneumonia, while not preventing infection, and this effect should be further studied. An alternative explanation for what we have observed is a possible effect in preventing a proportion of recipients of neuraminidase inhibitors from seroconverting into asymptomatic influenza cases. This notion would explain the observed effects of neuraminidase inhibitors on serious complications and their interruption of transmission in households during seasonal influenza. Whichever explanation is chosen, prophylactic use of neuraminidase inhibitors in a serious epidemic or a pandemic could enhance vulnerability to infection by preventing seroconversion and facilitating the selection of mutant viruses resistant to neuraminidase inhibitors. We do not see a role for the use of neuraminidase inhibitors in seasonal influenza, since the evidence shows that they are ineffective against influenza-like illness. Influenza-like illness is the syndrome presenting to the physician who has no way of knowing whether the case in front of him or her is caused by influenza A, B, or other agents—eg, respiratory syncytial viruses and parainfluenza viruses—unless there is up-to-date information on local influenza viral circulation in a confirmed serious influenza epidemic (or a pandemic). In this instance, the likelihood that the presenting case is caused by influenza A or B (in other words that it is real influenza) is higher, with a consequent higher efficacy and effectiveness and a narrowing of the gap between the two.

The data we identified on effects on avian influenza related only to oseltamivir. This drug was used against three subtypes of avian infuenza viruses with proven bird-to-human and human-to-human transmission: A/H5N1, A/H7N7, and A/H7N3. The virological and transmission profile of avian H5N1 influenza is not clear. One review[65] reports that experience from the cases of avian influenza transmitted to people in southeast Asia suggests that viral shedding commences before symptoms appear and ceases after 48 h from symptoms onset. The WHO-led review[66] of H5N1 influenza cases suggests that viral shedding and infectivity of index cases could be protracted. What seems clear, however, is that viral load can be up to ten times greater than in seasonal influenza.[66] In the outbreaks in southeast Asia, use of oseltamivir was not associated with any obvious effect on mortality, although this finding could be the result of late commencement of therapy and high initial viral load. Resistance to oseltamivir was detected in up 16% (seven of 43) of children given the drug[66] (this is consistent with evidence from Japan[70]) and in two of eight Vietnamese people aged 8–35 years.[71] The apparently common feature favouring the selection of resistant viruses is immunological naivety to the infecting viral subtype.

A large outbreak of avian A/H7N7 influenza with bird-to-human and human-to-human transmission took place in chicken farms in the Netherlands between February and June, 2003. 85 of the 453 people who reported symptoms (mainly influenza-like illness or conjunctivitis, or both) had A/H7N7 isolated from their lacrimal fluid or upper airway swabs, or both. Among other measures, post-exposure prophylaxis with oseltamivir 75 mg was started. 90 people in the case registry probably had prophylactic treatment. Infection with avian influenza virus was detected in one of 38 (3%) people who used oseltamivir, compared with five of 52 (10%) who reported that they had not taken prophylactic medication. The difference was not significant (p=0·38), probably because of small numbers and the late nature of the commencement of post-exposure prophylaxis.[67] A similar outbreak of A/H7N3 took place in British Columbia, Canada, in 2004. 12 possible cases (22% of total) reported taking prophylactic oseltamivir at symptom onset, and 11 (20%) received oseltamivir for treatment. Maximum duration of oseltamivir use is thought to have been 12 weeks.[2] The remaining 22 patients with suspected cases were identified more than 48 h after onset or refused treatment. All recovered fully.[68] The effects of oseltamivir were not formally studied and data on the effectiveness of oseltamivir are insufficient to reach a conclusion.

In short, we could find no credible evidence of the effects of neuraminidase inhibitors on avian influenza and, not surprisingly, no evidence of their effects on pandemic influenza viruses. As viral load and virulence of pandemic viruses are considerably higher than those of seasonal influenza viruses, the use of neuraminidase inhibitors in a serious epidemic or pandemic should not be considered without concomitant measures, such as barriers, distance, and personal hygiene. The possible inability of neuraminidase inhibitors to prevent infection and to suppress viral nasal excretion raise doubts as to their effectiveness in interrupting viral spread, although they might have a role in addressing symptoms and complications. However, symptomatic relief and an overestimation of the capacity of antivirals to prevent illness could alter the behaviour of recipients and favour viral spread. Over-reliance on a pharmacological solution to the ravages of influenza may impede the development and implementation of broader intervention strategies based on public-health measures.

Contributors

T Jefferson and V Demicheli designed the study, wrote the protocol, and extracted data. A Rivetti did supplementary searches. T Jefferson, D Rivetti, and V Demicheli applied inclusion criteria. M Jones and C Di Pietrantonj undertook the meta-analysis and did statistical testing. T Jefferson and D Rivetti wrote the final report. All authors contributed to both protocol and final report.

Conflict of interest statement

T Jefferson owned shares in GlaxoSmithKline (1998–2004) and received consultancy fees from Sanofi-Synthelabo (2002) and Roche (1997–99). All other authors declare that they have no conflict of interest.

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