Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto

Summary

Background Despite widespread use, questions remain about the efficacy of oseltamivir in the treatment of influenza. We aimed to do an individual patient data meta-analysis for all clinical trials comparing oseltamivir with placebo for treatment of seasonal influenza in adults regarding symptom alleviation, complications, and safety.

Methods We included all published and unpublished Roche-sponsored randomised placebo-controlled, double-blind trials of 75 mg twice a day oseltamivir in adults. Trials of oseltamivir for treatment of naturally occurring influenza-like illness in adults reporting at least one of the study outcomes were eligible. We also searched Medline, PubMed, Embase, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov trials register for other relevant trials published before Jan 1, 2014 (search last updated on Nov 27, 2014). We analysed intention-to-treat infected, intention-to-treat, and safety populations. The primary outcome was time to alleviation of all symptoms analysed with accelerated failure time methods. We used risk ratios and Mantel-Haenszel methods to work out complications, admittances to hospital, and safety outcomes.

Findings We included data from nine trials including 4328 patients. In the intention-to-treat infected population, we noted a 21% shorter time to alleviation of all symptoms for oseltamivir versus placebo recipients (time ratio 0·79, 95% CI 0·74–0·85; p<0·0001). The median times to alleviation were 97·5 h for oseltamivir and 122·7 h for placebo groups (difference –25·2 h, 95% CI –36·2 to –16·0). For the intention-to-treat population, the estimated treatment effect was attenuated (time ratio 0·85) but remained highly significant (median difference –17·8 h). In the intention-to-treat infected population, we noted fewer lower respiratory tract complications requiring antibiotics more than 48 h after randomisation (risk ratio [RR] 0·56, 95% CI 0·42–0·75; p=0·0001; 4·9% oseltamivir *vs* 8·7% placebo, risk difference –3·8%, 95% CI –5·0 to –2·2) and also fewer admittances to hospital for any cause (RR 0·37, 95% CI 0·17–0·81; p=0·013; 0·6% oseltamivir, 1·7% placebo, risk difference –1·1%, 95% CI –1·4 to –0·3). Regarding safety, oseltamivir increased the risk of nausea (RR 1·60, 95% CI 1·29–1·99; p<0·0001; 9·9% oseltamivir *vs* 6·2% placebo, risk difference 3·7%, 95% CI 1·8–6·1) and vomiting (RR 2·43, 95% CI 1·83–3·23; p<0·0001; 8·0% oseltamivir *vs* 3·3% placebo, risk difference 4·7%, 95% CI 2·7–7·3). We recorded no effect on neurological or psychiatric disorders or serious adverse events.

Interpretation Our findings show that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting.

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Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK (J Dobson MSc, Prof S Pocock PhD); **Department of Pediatrics, Microbiology, Medicine and Neurosurgery, University of Alabama at Birmingham, Birmingham, AL, USA** (Prof R J Whitley MD); **and Department of Epidemiology, University of Michigan School of Public Health, MI, USA** (Prof A S Monto MD)

Correspondence to:
Prof Arnold S Monto, Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109-2029, USA
asmonto@umich.edu

Introduction

Neuaraminidase inhibitors were developed in the 1990s as a novel approach to prophylaxis and treatment of influenza.[1] Zanamivir and oseltamivir selectively block the conserved enzymatic activity of all influenza viruses, making them useful in prophylaxis and treatment for both seasonal and pandemic disease.[2–4] The oral drug oseltamavir has received more attention, especially regarding pandemic preparedness.[5] The drug was widely used for treatment during the 2009 influenza pandemic. However, questions persist about the efficacy of oseltamivir, with some investigators even suggesting that the drug has no antiviral effect.[6] Concerns also exist about the drug's adverse effects and whether these outweigh the benefits. Such conclusions arose in a meta-analysis based on clinical trial study reports rather than individual patient data.[6]

To explore these issues further, we did a meta-analysis of all available randomised treatment trials of oseltamivir in adults. Our meta-analysis is the first to use individual patient data and includes both published and unpublished trials thereby overcoming previous concerns regarding potential publication bias. We focused on both intention-to-treat analyses and analyses restricted to individuals with documented influenza infection. We assessed possible side effects of oseltamivir and the incidence of complications.

Methods

Search strategy and selection criteria

We included all published and unpublished Roche-sponsored randomised placebo-controlled, double-blind trials of oseltamivir treatment in adult influenza.[7–12] Individual patient data were provided by Roche by use of

	Intention to treat infected					Intention to treat				
	Oseltamivir N	Placebo N	Estimates of median time and their difference (h)			Oseltamivir N	Placebo N	Estimates of median time and their difference (h)		
			Oseltamivir	Placebo	Difference			Oseltamivir	Placebo	Difference
M76001	681	355	96·3	120·5	−24·2	933	473	97·7	114·7	−17·1
WV15819_876_978	223	254	150·0	174·9	−24·9	358	375	139·2	149·0	−9·8
WV15670	157	161	87·4	116·5	−29·1	240	235	97·6	116·1	−18·5
WV15812_872	118	133	151·5	161·0	−9·5	199	202	143·0	163·0	−20·0
JV15823	121	130	70·0	93·3	−23·3	152	158	63·1	81·8	−18·6
WV15671	121	128	71·5	103·3	−31·7	204	200	76·3	97·0	−20·7
WV16277	119	109	80·3	99·3	−19·0	226	225	88·8	100·3	−11·5
WV15730	19	19	78·2	143·9	−65·8	31	27	74·5	109·8	−35·3
WV15707	6	6	53·3	31·3	22·0	17	9	88·8	56·2	32·7
Overall*	1565	1295	97·5	122·7	−25·2 (−36·2 to −16·0)	2360	1904	99·4	117·2	−17·8 (−27·1 to −9·3)

*Medians and differences in medians for individual trials are from Kaplan-Meier estimates. The overall estimated medians, differences (and 95% CI) are from the accelerated failure time model adjusted for trial.

Table 1: **Estimates of median time to alleviation of all symptoms by treatment group in the intention-to-treat infected and intention-to-treat populations, both overall and for each trial**

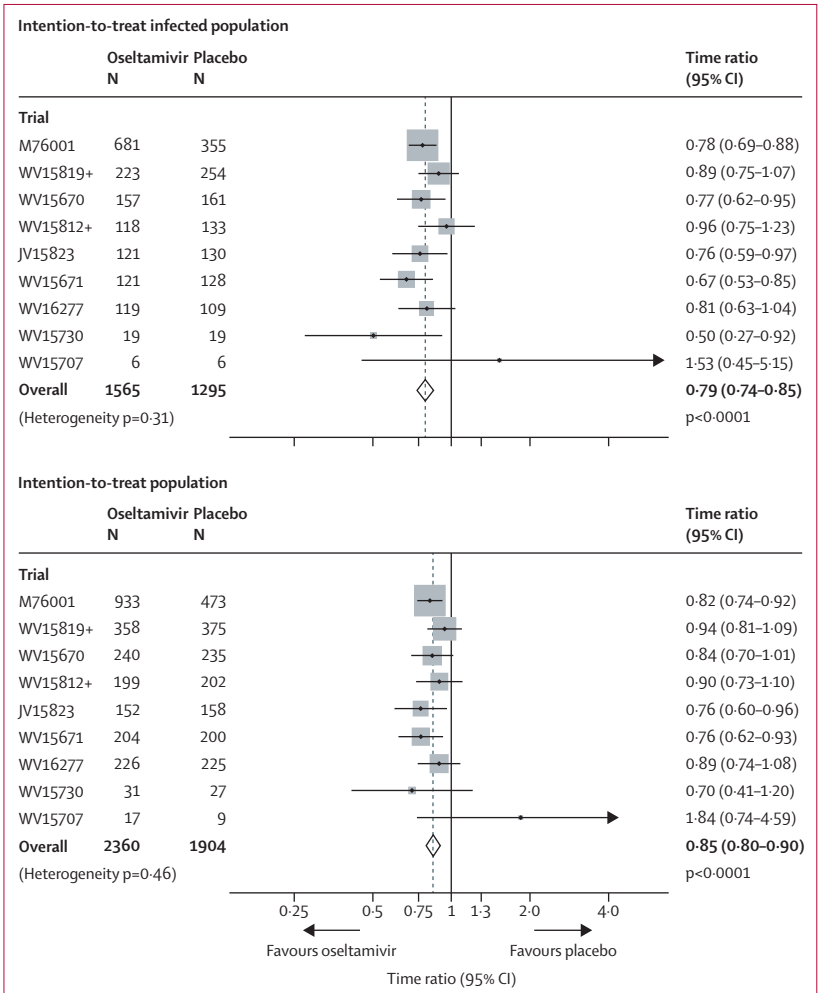

Figure 1: **Fixed effect meta-analysis for time to alleviation of all symptoms**
The overall time ratio is calculated from an accelerated failure time model adjusted for trial.

secure web-access. Roche provided data clarifications but had no involvement in the design, conduct, or reporting of the meta-analysis. All trials satisfied relevant good clinical practice criteria, with approval from ethics committees and regulatory authorities. Furthermore, data quality was assured by thorough data audits by the US Food and Drug Administration (FDA). Additionally, we searched Medline (and PubMed), Embase, the Cochrane Central Register for Controlled Trials, and the ClinicalTrials.gov trials register for other relevant trials published before Jan 1, 2014 (appendix pp 1–2). We incorporated all trials of treatment in adults included in a previous meta-analysis plus one additional trial (JV15823).[6] We excluded a Chinese treatment trial in adults because individual patient data were not available.[13] We also excluded one very small trial in adults and children (n=19).[14] After extensive searches by both Jefferson and colleagues[6] and ourselves, no other adult trials of oseltamivir treatment were identified.

Study design

The nine trials were done between 1997 and 2001. Eligible participants were within 36 h of feeling unwell, with a fever (≥38°C if aged <65 years, ≥37·5°C if aged ≥65 years), and with at least two influenza symptoms (one respiratory: cough, sore throat or coryza; and one constitutional: headache, myalgia, sweats or chills, or fatigue). Participants received oseltamivir or placebo for 5 days at 12 h intervals. Total follow-up was 21 days. Recruitment began upon detection of a local influenza outbreak. Participants received the first dose of the randomised study drug during their enrolment clinic visit. Participants were subsequently identified as influenza-infected by a positive culture from a nasal or throat swab (viral shedding at baseline or during follow-up) or four-fold or greater increase from baseline in antibody titre (trial definition). In some trials, virus culture was not done at all centres (in these centres

influenza infection was based on antibody titre rise only). We focused on 75 mg twice a day of oseltamivir because this is the standard prescribed dose.

Efficacy analyses were first for participants getting at least one dose of study drug and who were identified as influenza-infected (intention-to-treat infected population), and then repeated for the intention-to-treat population, which included all treated participants. Both these population definitions were those used in the individual trials. A few participants (18 in the oseltamivir group and 12 in the placebo group) were excluded because they received no study drug and had no follow-up data. Main analyses were also repeated in the intention-to-treat-not infected population. Safety analyses were by treatment received and in participants taking at least one dose of study drug (safety population). Follow-up was from first study drug intake, as was done in individual trial reports. For brevity we refer to randomisation as time of randomisation and first study drug intake were very similar.

Outcomes

The primary outcome was time to alleviation of all symptoms. Seven influenza symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats) were scored as absent, mild, moderate, or severe. Alleviation was defined to arise when all symptoms scored as absent or mild, and remained so for at least 21·5 h.

The main complication was lower respiratory tract complication more than 48 h after randomisation requiring antibiotics (preferred terms containing "bronchitis", "pneumonia", "lower respiratory tract infection"). Lower respiratory tract complications requiring antibiotics might better represent clinically relevant disease, and oseltamivir would be unlikely to affect lower respiratory tract complications before 48 h. The 48 h cut-off was previously used in some of the individual trial reports. Sensitivity analyses included complications occurring before 48 h. Participants taking antibiotics at baseline were excluded. Diagnosis of complications was based on participant report and the investigator's clinical judgment. No diagnostic tests were needed. We also analysed admittance to hospital for any cause from randomisation as an indicator of complications.

Safety outcomes included death, treatment withdrawals, treatment withdrawals due to adverse events, all adverse events, serious adverse events, adverse events by body system class (including psychiatric disorders and neurological disorders), and preferred terms nausea, vomiting, and diarrhoea.

Statistical analyses

In view of the similar study designs of the trials, we used fixed-effect methods of meta-analysis. We noted little statistical heterogeneity, and sensitivity analyses with random effect methods for key findings gave very similar results. For time to alleviation of all symptoms, we initially assessed Kaplan-Meier plots by treatment group and we obtained a treatment effect estimate (time ratio) from a log-logistic accelerated failure time model adjusted for trial.[15] We did not use proportional hazards models because non-proportionality of hazards was evident. We estimated treatment difference in median time to alleviation of symptoms adjusted for trial along with a bootstrap confidence interval (2000 repetitions, stratified by trial and treatment group).

We assessed statistical heterogeneity in time ratios across trials by a likelihood ratio test. As a sensitivity analysis, separate accelerated failure time models were fitted for each trial and log time ratios were meta-analysed with inverse-variance weighting. We did pre-specified exploratory subgroup analyses for age, high-risk participants, time from symptom onset to randomisation, virus type, and total baseline symptom score. We did likelihood ratio tests of interaction.

We explored the difference between treatment groups in the pooled Kaplan-Meier estimates of the proportions with alleviation of all symptoms at 12 h, 24 h, then every 24 h to establish when a significant difference became apparent.

See Online for appendix

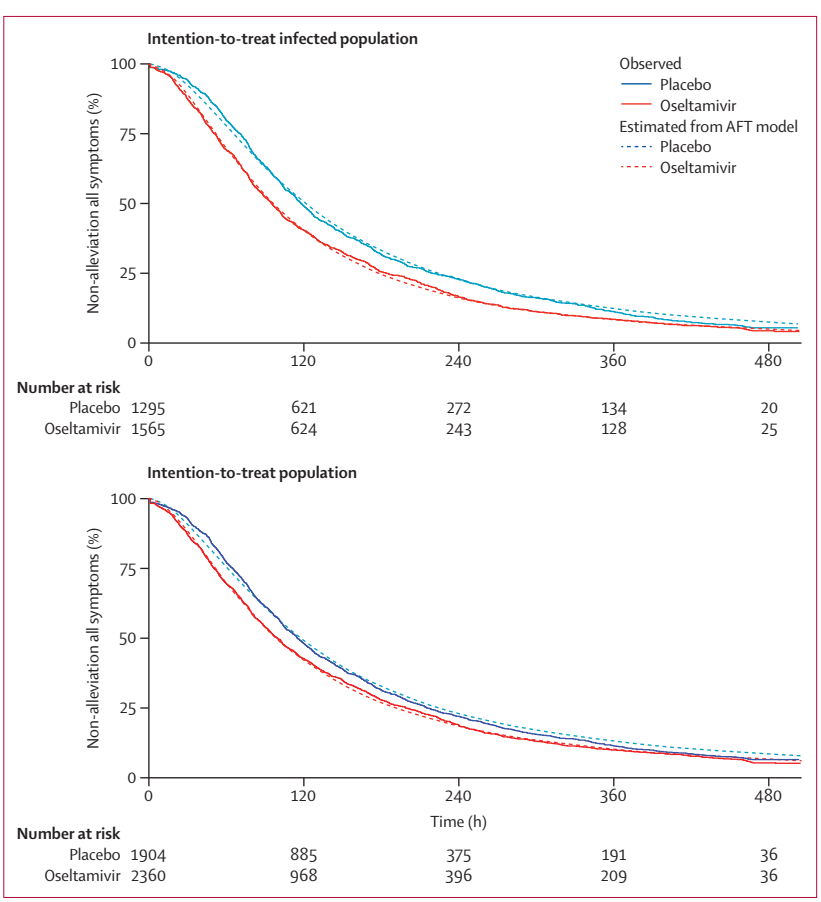

Figure 2: **Overall Kaplan-Meier curves and estimated survival curves from AFT model (adjusted for trial) by treatment group for time to alleviation of all symptoms in all trials combined**
AFT=accelerated failure time.

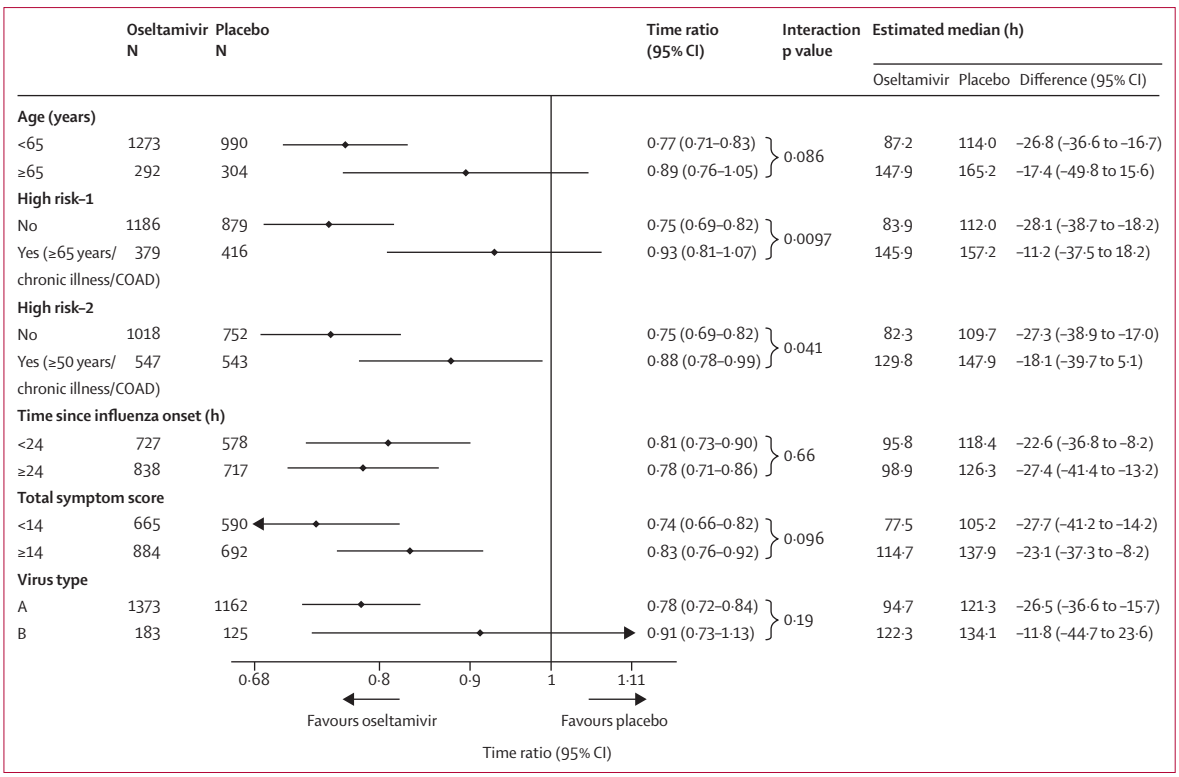

Figure 3: **Subgroup analyses for time to alleviation of all symptoms in the intention-to-treat infected population**
COAD=chronic obstructive airways disease. Estimated median (h)=estimated median time to alleviation of all symptoms from accelerated failure time model adjusted for trial. Diff (95% CI)=the difference in the estimated medians with bootstrap 95% CI.

Binary outcomes (eg, complications and adverse events) were meta-analysed with risk ratios and a Mantel-Haenszel fixed effect approach without continuity correction.[16,17] We excluded trials with no events in both groups and did χ^2 tests of heterogeneity. To obtain an overall risk difference, we applied the overall risk ratio (and 95% CI) to the pooled placebo group risk to calculate a risk difference and 95% CI.[17,18] Exploratory subgroup analysis for the lower respiratory tract complication outcome used inverse-variance weighting to assess heterogeneity between subgroups.

For complication and adverse event outcomes, we excluded events arising beyond 28 days after randomisation. We analysed adverse events separately for on treatment and off treatment periods. On treatment was defined as up to 2 days after the last dose of study drug. For psychological and neurological disorders, we did a sensitivity analysis in participants infected with influenza only because these events might be directly related to influenza symptoms. Additionally, the two trials with a 150 mg twice a day oseltamivir dose compared with placebo were included to investigate potential associations between dose and response. For nausea and vomiting, we also did separate analyses for influenza-infected and non-influenza infected participants.

Because post-baseline data was used in the definition of influenza infection, we repeated efficacy analyses for participants who were influenza-infected on the basis of viral shedding at baseline only. All analyses used Stata version 13.1.

Role of the funding source

The meta-analysis was funded by the Multiparty Group for Advice on Science (MUGAS) who assembled a multidisciplinary team to examine the overall data from trials of oseltamivir in adults. The team agreed an individual patient data analysis was the most robust approach, and to cover the costs the MUGAS Board applied for an unrestricted grant from Roche. This unrestricted grant stipulates that Roche would not be involved in the actual review process in any way other than providing the requested data dictionaries and datasets. The results were not shared with Roche until the analysis was completed. The London School of Hygiene & Tropical Medicine received a grant from MUGAS to partly fund Joanna Dobson's salary while she worked on this project. RJW and AMS received travel expenses from MUGAS for investigator meetings in London.

Results

In the intention-to-treat population 2402 participants were randomly assigned to receive 75 mg oseltamivir twice a day and 1926 to placebo (one trial had 2:1 randomisation). Of these, 1591 (66%) in the oseltamivir

group and 1302 (68%) in the placebo group were influenza-infected constituting the intention-to-treat infected population. The appendix shows characteristics of the nine included trials (appendix p 3). Most participants had influenza virus type A (2558/2893 [88%]); A-H3N2 was the main strain (appendix p 4). The safety population comprised 2401 participants on oseltamivir and 1917 on placebo. Two trials (protocol numbers WV15819_876_978 and WV15707) were in elderly participants (≥65 years), and one was in participants with chronic cardiac or respiratory disease or both (WV15812_872). Three trials did not meet planned recruitment targets but were still included (WV16277, WV15730, and WV15707). Baseline characteristics were balanced between treatment groups for each trial (appendix p 5).

64 (1·5%) of 4328 participants were missing time to alleviation of all symptoms. The median time to alleviation of symptoms in the placebo group varied across trials (table 1) and was longer in the trials with participants with chronic illnesses and in elderly people. In the intention-to-treat infected population, there was a 21% shorter time to alleviation of all symptoms for oseltamivir compared with placebo (time ratio 0·79, 95% CI 0·74–0·85; p<0·0001; figure 1). Across all trials, the estimated median time to alleviation of all symptoms was 97·5 h for oseltamivir, 122·7 h for placebo (difference –25·2 h, 95% CI –36·2 to –16·0). In the intention-to-treat population, the estimated time reduction attenuated to 15% but remained highly significant (time ratio 0·85, 95% CI 0·80–0·90; p<0·0001). The treatment difference in median time to symptom alleviation became –17·8 h (95% CI –27·1 to –9·3). The accelerated failure time model provided a good fit to the data (figure 2). Sensitivity analyses with a two-stage meta-analysis method produced similar results (data not shown). We noted no heterogeneity in time ratios across trials (interaction p=0·31 [intention-to-treat infected], p=0·46 [intention-to-treat]). In the intention-to-treat-not infected population, the estimated time ratio was close to unity (time ratio 0·99, 95% CI 0·88–1·12; p=0·91), so only participants identified as influenza-infected benefited from oseltamivir.

In exploratory analyses with pooled Kaplan-Meier estimates of percentage without symptoms, a marked treatment difference emerged by 24 h after randomisation (intention-to-treat infected: difference 5·2%, 95% CI 3·4–7·0; p<0·0001; intention-to-treat: difference 4·6%, 95% CI 3·1–6·2; p<0·0001).

Figure 3 shows exploratory subgroup analyses for time to alleviation of all symptoms in the intention-to-treat infected population. The time ratio of oseltamivir versus placebo recipients was attenuated for high-risk participants (≥65 years or in chronic illness trial or chronic obstructive airways disease at baseline; interaction p=0·0097). Findings of an alternative high-risk subgroup analysis, with participants aged 50 to 64 years also as high risk, were supportive of this finding. For age, time from influenza onset, total symptom score, and virus type, we noted no heterogeneity in time ratios.

In the intention-to-treat infected population, we recorded a lower respiratory tract complication arising after 48 h after randomisation requiring antibiotics in 65 (4·2%) of 1544 participants given oseltamivir and 110 (8·7%) of 1263 participants given placebo (figure 4). An estimated 44% reduction in risk of lower respiratory tract complications was attributable to oseltamivir treatment (RR 0·56, 95% CI 0·42–0·75; p=0·0001), with absolute risk difference of –3·8% (95% CI –5·0 to –2·2). Components of this outcome were 56 (3·6%) versus 87 (6·9%) bronchitis, nine (0·6%) versus 21 (1·7%) pneumonia, and one (0·1%) versus four (0·3%) lower respiratory tract infection in oseltamivir and placebo groups, respectively. Risk ratios for pneumonia and bronchitis were 0·40 (95% CI 0·19–0·84; p=0·015) and 0·62 (95% CI 0·45, 0·85; p=0·0030), respectively. In the intention-to-treat population, 105/2330 (4·5%) oseltamivir and 147/1872 (7·9%) placebo subjects experienced a lower

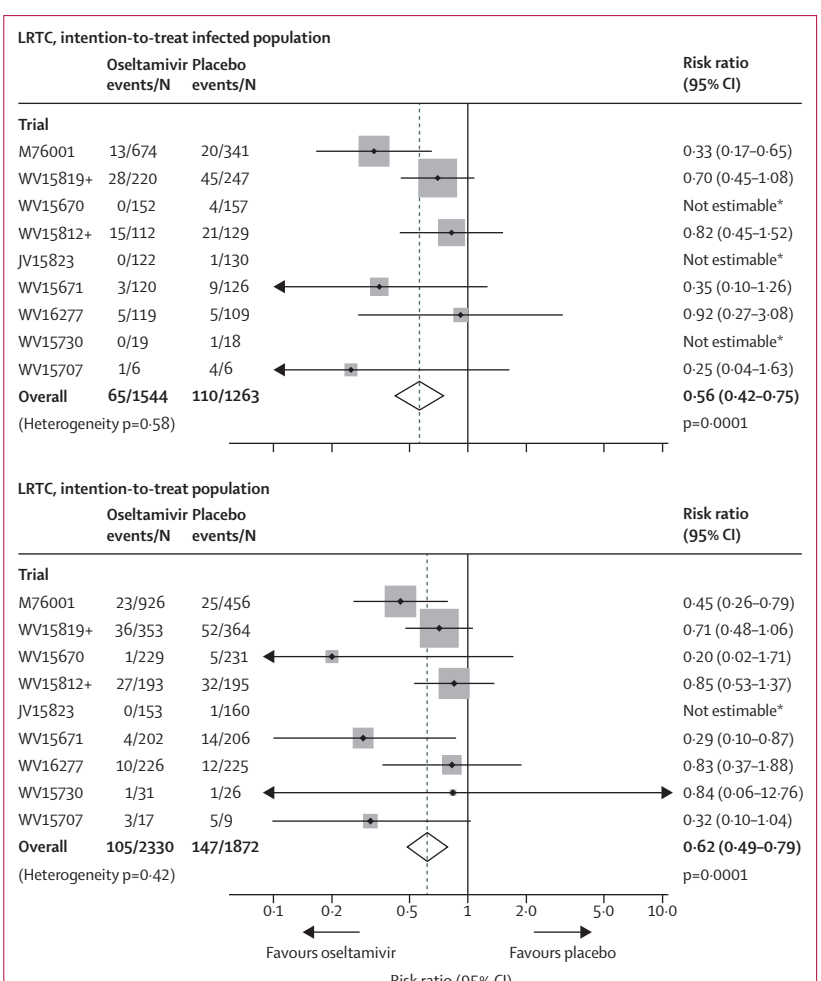

Figure 4: **LRTC, intention-to-treat infected, and intention-to-treat population**
LRTC=lower respiratory tract complications. Events=number of participants who had one or more events. *No events in oseltamivir group. The trial still contributes to the overall estimates.

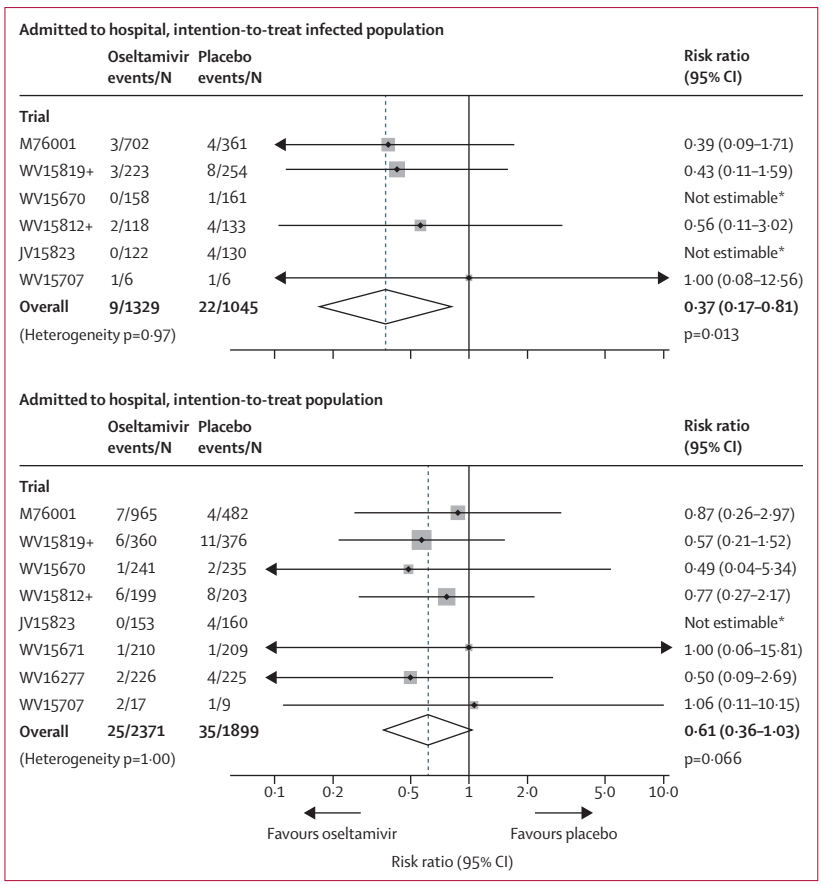

Figure 5: **Admittance to hospital, intention-to-treat infected, and intention-to-treat population**
Events=number of participants who had one or more events. *No events in oseltamivir group. The trial still contributes to the overall estimates.

respiratory tract complication with risk ratio attenuated to 0·62, 95% CI 0·49, 0·79; p=0·0001; risk difference: –3·0%, 95% CI –4·0 to –1·7. For pneumonia and bronchitis the intention-to-treat risk ratios became 0·34 (95% CI 0·18–0·64; p=0·0009, 13 [0·6%] *vs* 32 [1·7%]) and 0·71 (95% CI 0·54–0·93; p=0·011, 90 [3·9%] *vs* 111 [5·9%]), respectively. We noted no effect on lower respiratory tract complications in the intention-to-treat-not infected population (RR 0·82, 95% CI 0·53–1·26; p=0·36). We recorded no statistical heterogeneity across trials.

An exploratory subgroup analysis of lower respiratory tract complications in the intention-to-treat infected population had a relative risk of 0·70 (95% CI 0·49–0·98) in high-risk participants (45/371 in the oseltamivir group *vs* 72/403 in the placebo group) versus 0·39 in others (95% CI 0·23–0·66; 20/1173 in the oseltamivir group *vs* 38/860 in the placebo group; interaction p=0·070).

The addition of lower respiratory tract complications starting before 48 h (intention-to-treat infected: extra 15/1544 *vs* 13/1263; intention-to-treat: extra 26/2330 *vs* 19/1872) attenuated the risk ratios for both intention-to-treat infected and intention-to-treat populations but they remained highly significant (intention-to-treat infected: RR 0·61, 95% CI 0·47–0·79; p=0·0002; intention-to-treat: RR 0·68, 95% CI 0·55–0·85; p=0·0005).

A sensitivity analysis for time to alleviation of all symptoms, restricting analysis to participants who were influenza-infected on the basis of viral shedding at baseline only gave an estimated time ratio similar to that in the intention-to-treat infected analysis (time ratio 0·77, 95% CI 0·71–0·84; p<0·0001). We noted similar results for lower respiratory tract complications (RR 0·59, 95% CI 0·40–0·88; p=0·0089).

In the intention-to-treat infected population, nine (0·6%) of 1591 participants had to be admitted to hospital for any cause versus 22 (1·7%) of 1302 participants given placebo (figure 5), an estimated 63% risk reduction (RR 0·37, 95% CI 0·17–0·81; p=0·013) with risk difference of –1·1% (95% CI –1·4 to –0·3). In the intention-to-treat population, the risk ratio attenuated and was no longer statistically significant (25/2402 oseltamivir *vs* 35/1926 placebo; RR 0·61, 95% CI 0·36–1·03; p=0·066). In the intention-to-treat-not infected population, the estimated risk ratio was close to unity (16/811 oseltamivir *vs* 13/624 placebo; RR 1·01, 95% CI 0·47–2·15; p=0·99). The causes of admittance to hospital covered many disorders with no discernible pattern (data not shown). Seven participants were admitted to hospital because of pneumonia (two in the oseltamivir group and five in the placebo group) in the intention-to-treat infected population. We noted no statistical heterogeneity across trials. One participant on placebo and not influenza-infected died because of respiratory failure.

Table 2 shows key findings for on treatment adverse events (appendix p 6 shows all adverse events and appendix p 7 shows serious adverse events and cardiac disorders). We noted highly significant excesses on oseltamivir for nausea, vomiting, and all gastrointestinal disorders. By contrast oseltamivir had significantly less diarrhoea, infections and infestations, and respiratory, thoracic and mediastinal disorders. Participants given oseltamivir had fewer cardiac disorders, and more injury and poisoning than did those given placebo, but numbers of events were small. We noted no discernible cause-specific pattern in cardiac disorders and only three participants (one in the oseltamivir group and two in the placebo group) had cardiac disorders deemed serious adverse events. We recorded no overall treatment difference in on treatment serious adverse events. There was no evidence of a treatment difference for neurological or psychiatric disorders in the safety population or in participants infected with influenza. The excess of nausea and vomiting arose both in participants influenza-infected and in others, although the risk ratio for vomiting was lower and non-significant in those not infected than in those with influenza infection. We noted no heterogeneity across trials for any adverse events (data not shown).

The incidence of on treatment psychiatric adverse events was numerically higher on the 150 mg twice a day

	Number of events		Overall risk ratio (95% CI)	p value	Placebo group risk (%)*	Oseltamivir group risk (%)†	Risk difference (95% CI)
	Oseltamivir (n=2401)	Placebo (n=1917)					
All adverse events	1033	819	0·97 (0·91 to 1·04)	0·41	42·7	41·5	−1·2% (−4·0 to 1·8)
Serious adverse events	21	22	0·79 (0·43 to 1·47)	0·46	1·1	0·9	−0·2% (−0·7 to 0·5)
Gastrointestinal disorders	574	370	1·21 (1·07 to 1·36)	0·0019	19·3	23·3	4·0% (1·4 to 6·9)
Nausea	247	118	1·60 (1·29 to 1·99)	<0·0001	6·2	9·9	3·7% (1·8 to 6·1)
Vomiting	201	63	2·43 (1·83 to 3·23)	<0·0001	3·3	8·0	4·7% (2·7 to 7·3)
Diarrhoea	147	147	0·75 (0·60 to 0·95)	0·016	7·7	5·8	−1·9% (−3·1 to −0·4)
Cardiac disorders	13	20	0·49 (0·25 to 0·98)	0·043	1·0	0·5	−0·5% (−0·8 to −0·0)
Infections and infestations	231	217	0·84 (0·70 to 1·00)	0·049	11·3	9·5	−1·8% (−3·4 to −0·0)
Injury and poisoning	15	4	3·37 (1·08 to 10·47)	0·036	0·2	0·7	0·5% (0·0 to 2·0)
Respiratory, thoracic, and mediastinal disorders	158	143	0·74 (0·60 to 0·93)	0·0081	7·5	5·5	−1·9% (−3·0 to −0·6)
Neurological disorders	124	93	1·00 (0·76 to 1·30)	0·97	4·9	4·8	−0·0% (−1·2 to 1·5)
Psychiatric disorders	11	13	0·62 (0·26 to 1·45)	0·27	0·7	0·4	−0·3% (−0·5 to 0·3)
Additional analyses in influenza-infected participants‡							
Neurological disorders	91	73	0·95 (0·70 to 1·29)	0·76	5·6	5·4	−0·3% (−1·7 to 1·6)
Psychiatric disorders	10	9	0·81 (0·31 to 2·08)	0·65	0·7	0·6	−0·1% (−0·5 to 0·7)
Nausea	172	85	1·60 (1·24 to 2·07)	0·0003	6·5	10·5	3·9% (1·6 to 7·0)
Vomiting	155	41	3·00 (2·11 to 4·26)	<0·0001	3·2	9·5	6·3% (3·5 to 10·3)
Additional analyses in participants without influenza§							
Nausea	75	33	1·67 (1·12 to 2·49)	0·011	5·3	8·9	3·6% (0·7 to 7·9)
Vomiting	46	22	1·49 (0·90 to 2·46)	0·12	3·6	5·3	1·7% (−0·4 to 5·2)

Events=number of participants who had one or more events. *Placebo group risk is calculated using all trials (including trials with no outcomes in each group).†Oseltamivir group risk and risk difference (95% CI) obtained by applying overall risk ratio and 95% CI to pooled placebo group risk. ‡n=1590 in the oseltamivir group and n=1299 in the placebo group. §n=811 in the oseltamivir group and n=618 in the placebo group

Table 2: **Meta-analyses findings for key on treatment adverse events in the safety population, by treatment received**

dose than placebo but numbers of events were small (150 mg [8/447] vs placebo [3/439] RR 2·61, 95% CI 0·70–9·78; p=0·15). The 150 mg dose did not seem to affect neurological adverse events (data not shown).

Fewer off treatment serious adverse events arose in participants given oseltamivir (RR 0·23, 95% CI 0·09–0·58; p=0·0018), but numbers of events were small (6/2401 in the oseltamivir group *vs* 22/1917 in the placebo group; appendix p 7). No other off treatment adverse events showed a treatment difference (data not shown). Treatment withdrawal rates were similar (117/2401 in the oseltamivir group *vs* 79/1917 in the placebo group; RR 1·04, 95% CI 0·78, 1·39; p=0·78) as was treatment withdrawal due to an adverse event (36/2401 in the oseltamivir group *vs* 33/1917 in the placebo group; RR 0·76, 95% CI 0·46–1·25; p=0·28).

Discussion

Our findings show that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting.

Randomised trials done for licensing a new treatment typically focus on essential issues of efficacy and safety. The development of treatments for influenza is no exception. Not all questions related to eventual use of a drug can be answered by such trials. These issues are usually addressed in subsequent observational studies, which are complicated by potential selection bias in who receives the intervention.[19,20] Thus, randomised trials provide the best evidence to assess events that arise with sufficient frequency. Insight can be increased by combining evidence across trials providing their designs are similar. Such meta-analyses are best done by use of individual patient data; advantages include more thorough analysis of outcomes (eg, time to event), exploring patient subgroups, the ability to check data quality, and performance of sensitivity analyses on key outcomes.[21]

After extensive searches by both Jefferson and colleagues[6] and ourselves, we excluded just two relevant oseltamivir treatment trials in adults from our meta-analysis: a trial in 451 Chinese adults that concluded "oseltamivir was effective and well tolerated", and a trial that recruited only 19 adults and children (four to early oseltamivir, eight to late oseltamivir, and seven to placebo) that concluded "time to 50% decrease in symptom severity, complete symptom resolution, and first negative

culture were shortest among the early treatment group".[13,14] Because these conclusions are broadly consistent with our findings, we believe our results based on individual patient data provide the best available evidence on oseltamivir treatment in adults. With regards to paediatric studies of oseltamivir treatment, a further individual patient data meta-analysis of three Roche-sponsored randomised trials plus two other randomised trials in children is underway and will be published separately.[22–25]

For the primary outcome of time to alleviation of all symptoms, we noted an absolute reduction of about 1 day in the intention-to-treat infected population, which was somewhat attenuated in the intention-to-treat population. These estimates are broadly compatible with those of observational studies and a previous meta-analysis.[6,20] A basic question is what primary population should be selected for analysis? In the pivotal studies for licensure, the intention-to-treat infected population was chosen, namely those participants actually having laboratory confirmed influenza by virus isolation or rise in antibody titre. The PCR technique for identifying influenza was not yet available. Parenthetically, intention-to-treat infected is the standard analysis used worldwide by regulatory authorities for licensure.[26]

The other approach we presented is the intention-to-treat population (ie, all treated patients whether infected or not), which inevitably dilutes estimates of any possible antiviral drug effect. The intention-to-treat population includes all randomly assigned participants and thus captures the overall drug exposure. However, the intention-to-treat infected population provides more direct insight into how the drug works in the disease being studied.

We recorded no reduction in time to symptom alleviation in participants not identified as being infected with influenza. Thus efficacy seems to be confined to the antiviral activity of the drug. Other investigators have only used the intention-to-treat population, which dilutes true efficacy, but does estimate effectiveness in a real-world setting in which some treated patients inevitably will not have influenza. Use of the intention-to-treat infected population was abandoned in a previous meta-analysis because slightly more placebo participants were documented as infected than were participants given oseltamivir, which investigators argued might introduce a bias.[6] We used sensitivity analyses to explore this issue; by classifying as infected only patients with virus identified at enrolment, we noted little change in time to alleviation results compared with our original intention-to-treat infected analysis.

Prevention of complications was not a pre-defined focus of each trial because of insufficient power; nevertheless, combined data for complications across all trials provide important evidence. Reductions in complications, admittance to hospital, and deaths have been addressed in observational studies, especially during the 2009 pandemic, but randomised evidence is more compelling.[19,20,27] Complication rates are low, but still significant risk reductions were detected both in the intention-to-treat infected and intention-to-treat populations. Identification of complications was not an aim of most studies—eg, pneumonia diagnosis did not have radiographic validation. To ensure complications were not simply differentially reported because of milder symptoms on oseltamivir, we studied only those requiring antibiotics. Bronchitis could be considered part of the overall influenza syndrome, but the same pattern of reduced complications also applies to pneumonia. We noted a significant 63% reduction in the risk of hospitalisation in the intention-to-treat infected population although this was attenuated and non-significant in the intention-to-treat population. This finding is more meaningful because oseltamivir has no effect on complications in participants who do not have influenza. Our results for complications and admittance to hospital are broadly consistent with those of observational studies and some previous meta-analyses of randomised trials.[20,28–31]

Findings of our meta-analysis confirm the clear harms of nausea and vomiting attributed to oseltamivir with estimated absolute increases of 3·7% for nausea and 4·7% for vomiting. These results are similar to anticipated rates with antimicrobial agents. Conversely, diarrhoea was more common in participants who took placebo. We did not find evidence of other harms caused by oseltamivir. Overall, we restricted our analysis to the licensed dose of 75 mg. We investigated a previous claim of a dose–response effect on incidence of psychiatric outcomes when the 150 mg dose was also investigated[6] and noted a numerical (but non-significant) excess for the 150 mg dose. At the 75 mg dose, the incidence of psychiatric outcomes was numerically lower than on placebo.

There are several limitations in our analyses. Respiratory complications were not a pre-defined primary outcome for the original trials and specific diagnostic tests were not necessary. So caution is warranted in interpreting these results, although incorporation of antibiotic use in the definition should enhance reliable reporting of complications. For both pneumonia and hospitalisation for any cause, we noted significant differences but numbers of events were small and so effect estimates are imprecise. The absence of a significant treatment difference for uncommon events might be explained by insufficient power to detect true effects even after data across studies was combined. This meta-analysis was for trials with a 5 day treatment duration.We did not study the benefits and harms of longer term use of oseltamivir (eg, in prophylaxis).

Oseltamivir's effectiveness in the intention-to-treat population might not be generalisable because the percentage of participants infected might vary across populations, both in these trials and in real-world

experience. The balance of benefits and harms becomes less favourable if more non-infected participants are treated with oseltamivir. Treatment strategies need to avoid this—eg, through availability of rapid diagnostic testing. This highlights the value of additionally reporting results for the intention-to-treat infected population.

In conclusion, oseltamivir accelerates clinical symptom alleviation in adults infected with influenza, and also reduces the risk of lower respiratory tract complications and admittances to hospital. Whether the magnitude of these benefits outweigh the harms attributed to nausea and vomiting needs to be carefully considered.

Contributors

JD did the statistical analyses and prepared data tables and figures. All authors contributed to writing of the manuscript and made substantial contributions to conception and design of the study, and analysis and interpretation of data.

Declaration of interests

ASM reports fees from Biocryst and Roche outside of the submitted work. RJW reports fees as a board member of Gilead Sciences, funding for travel from Roche to attend an Influenza Resistance Committee meeting, and fees as Associate Editor of the Journal of Infectious Diseases. JD and SP declare no competing interests.

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