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Oseltamivir and inhaled zanamivir as influenza prophylaxis in Thai health workers: a randomized, double-blind, placebo-controlled safety trial over 16 weeks

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Objectives: Long-term chemoprophylaxis using neuraminidase inhibitors may be needed during influenza epidemics but safety data are limited to several weeks. We sought to assess the tolerability of oseltamivir and zanamivir as primary prophylaxis over 16 weeks.

Methods: We conducted a parallel group, double blind, 2 (active drug):1 (placebo) randomized trial of oral oseltamivir/placebo or inhaled zanamivir/placebo over 16 weeks in healthy, Thai hospital professionals at two Bangkok hospitals. The primary endpoint was study withdrawal due to drug-related (possibly, probably, definitely) serious or adverse events (AEs) graded $\geq$2.

Results: Recruited subjects numbered 129 oseltamivir/65 placebo and 131 zanamivir/65 placebo. A total of 102 grade $\geq$2 AEs were reported or detected in 69 subjects: 23/129 (17.8%) versus 15/65 (23.1%) ($P=0.26$), and 23/131 (17.6%) versus 8/65 (12.3%) ($P=0.28$). Intercurrent infections/fevers [26/102 (25.5%)], abnormal biochemistry [25/102 (24.5%)] and gastrointestinal symptoms [18/102 (17.6%)] were the most frequently reported AEs. There were no drug-related study withdrawals. Eight serious AEs were all due to intercurrent illnesses. Laboratory, lung function and ECG parameters were similar between drugs and placebos.

Conclusions: Oseltamivir and zanamivir were well tolerated in healthy hospital professionals. Both drugs can be recommended for primary influenza prophylaxis for up to 16 weeks.

Keywords: neuraminidase inhibitors, pandemic, adverse event, tolerability

Introduction

Pandemic influenza A causes appreciable morbidity, mortality and disruption to normal life.[1,2] Chemoprophylaxis of key societal workers, such as healthcare professionals and firemen/women, needs to be effective and well tolerated.

The adamantanes, amantadine and rimantadine, are unsuitable for prophylaxis because of widespread resistance by the 2009 pandemic (pdm09) A/H1N1 and seasonal A/H3N2 viruses and most A/H5N1 clades[3–5] and poor prophylactic efficacy.[6,7]

The neuraminidase inhibitors oseltamivir and zanamivir are generally effective for preventing laboratory-confirmed influenza when used for limited time periods as primary[8–11] or post-exposure[12–14] prophylaxis in healthy adults,[8] individuals with comorbidities,[9] healthy soldiers[12] and households.[13,14] Systematic reviews are in accordance with the findings of individual studies.[7,15,16]

Oseltamivir resistance is uncommon in pdm09 A/H1N1,[17] A/H5N1[18] and A/H3N2[19] and common in seasonal A/H1N1,[20–22] but circulation of this virus has been replaced by pdm09 A/H1N1.[23] Resistance to oseltamivir has developed during prophylaxis of pdm09 A/H1N1[24,25] and during use as treatment for A/H5N1.[26] Molecular markers conferring zanamivir resistance are reported rarely in pdm09 A/H1N1, seasonal A/H1N1 and A/H3N2,[27,28] but their clinical significance is unclear.

Oseltamivir as prophylaxis is generally well tolerated, including in younger children.[29] Reported adverse event (AE) rates over 6 weeks include headache (~20%), nausea (~8%), fatigue (~8%), diarrhoea (3%) and vomiting (~2%).[30] In one large prophylaxis trial of two oseltamivir doses, rates of stopping oseltamivir due to AEs/intercurrent illnesses were similar to placebo (≤1.9%), but rates of nausea (12% and ~14% versus ~7%) and vomiting (~2.6% versus 0.8%) were significantly higher in the oseltamivir groups.[8] Poor tolerability was one important reason for reduced compliance (77% and 85%) with oseltamivir prophylaxis for 10 days in British school children.[31,32] Four of 42 health workers discontinued oseltamivir prophylaxis for a median time on oseltamivir of 3 months. Breakthrough, laboratory-confirmed influenza was observed in 24% and 17% of oseltamivir and influenza vaccine recipients, respectively (not significantly different).[33]

Bizarre behaviour, acute confusion, delusions/perceptual disturbances, self-harm and accidental deaths have been reported contemporaneously with oseltamivir treatment, mostly in Japanese adolescents.[34,35] These AEs were very rare (99/1 000 000 and 28/1 000 000 in Japanese children and adults, respectively), and occurred at similar rates between oseltamivir-treated and untreated patients.[36] Retrospective studies suggested oseltamivir was protective against acute psychiatric AEs.[37,38]

Zanamivir, delivered as a powder for oral inhalation by a Diskhaler, is also well tolerated. As prophylaxis, clinical AE rates over 28 days, e.g. headache (24%), throat discomfort (19%), cough (17%), and nausea and vomiting (2%), are very similar to those of placebo.[39] Serious AE (SAE) rates are low (<1%), similar to placebo, and have usually been related to influenza or underlying illnesses.[40] Similar findings have been documented in asthma and chronic obstructive pulmonary disease (COPD) sufferers and the elderly (≥65 years).[41] Inhaled zanamivir has been associated rarely with wheezing, including in non-asthmatics, shortness of breath, anaphylaxis, urticaria, and facial and oropharyngeal oedema.

Oseltamivir and zanamivir are registered as prophylaxis for up to 42 and 28 days, respectively, insufficiently long to cover pandemic influenza. Herein we report a 16 week prophylaxis study.

Materials and methods

Trial design

The aim of this randomized, parallel group, double-blind trial was to assess the tolerability and safety of daily oseltamivir relative to oseltamivir placebo, and daily inhaled zanamivir relative to zanamivir placebo, as primary prophylaxis over 16 weeks.

Participants

Subjects were health professionals who had to be literate, healthy males or females age >20 and <65 years, who provided written informed consent, and, if appropriate, agreed to use birth control.

Exclusion criteria were any of the following: (1) pregnant, trying to get pregnant or breast feeding; (2) asthma or COPD within the last 5 years requiring treatment; (3) any other chronic or acute disease requiring treatment; (4) study drug allergy; (5) haemoglobin <11 g/dL, neutropenia <1000/μL, platelet count <100 000/μL, creatinine clearance <30 mL/min (Cockcroft–Gault formula), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1.5× the upper limit of normal (ULN); (6) forced vital capacity (FVC) <80% of the predicted value for age and sex; (7) forced expiratory volume in 1 s (FEV_1)/FVC <75% (age <50 years) or <70% (≥50 years); (8) acutely abnormal chest X-ray; (9) ECG abnormality requiring immediate treatment/investigation; (10) participation in an investigational drug study within the previous 60 days; (11) received a live-attenuated influenza vaccine or any anti-influenza drug in the last 14 days (influenza vaccine was not allowed in the study); (12) alcohol or substance abuse; and (13) any psychiatric disease requiring treatment within the last 12 months or attempted suicide within last 5 years or a Hospital Anxiety and Depression Scale (HADS) score ≥8.

The study took place at Siriraj Hospital and the Hospital for Tropical Diseases (HTD), Bangkok, Thailand. Ethical approval was obtained from Siriraj Hospital, the Faculty of Tropical Medicine, and the Oxford University Tropical Ethics Committee. The trial is registered at ClinicalTrials.gov (no. NCT00980109).

Interventions

Doses were oseltamivir/placebo 75 mg once/day or zanamivir/placebo two inhalations once/day (5 mg/inhalation) for 16 weeks (112 days). Dosing was supervised during the working week by the study team and self-administered during weekends and holidays; a diary was used to record drug intake and symptoms. Subjects were instructed to replace missed doses only within 12 h. If ≥12 h had elapsed, this was considered a missed dose.

Outcomes

The primary endpoint was subjects withdrawing from the study because of serious or grade ≥2 AEs that were possibly, probably or definitely drug related.

The secondary endpoints included (1) the proportions of subjects who withdrew from the study because of SAEs or AEs graded ≥2 unlikely or not related to study drug/placebo; with any SAE or AE, irrespective of drug relationship or with any psychiatric AE; and (2) the total number of documented AEs at each follow-up visit. AEs were graded using the 2004 Division of AIDS Toxicity Table.[42]

Other endpoints included (1) respiratory function and (2) ECG changes over time, (3) oseltamivir and oseltamivir carboxylate (OC) pharmacokinetic profiles and their relationships with drug-related AEs, (4) development of influenza-like illness (ILI) and laboratory-confirmed influenza, and (5) susceptibility of isolated viruses to oseltamivir, zanamivir and adamantanes (genotypic and phenotypic assays).

Sample size

The sample size was based on placebo AE rates of 1%, 5%, 10%, 15%, 20% and 25%. For a power of 90% and two-sided α of 0.05, sample sizes of 100 (active arms) and 50 (placebo arms) would be able to detect corresponding differences in absolute AE rates of 14%, 19%, 22%, 25%, 26% and 27% (e.g. 1% versus 15%, etc.). With 100 subjects there was a 90% chance of observing a drug-related AE if its incidence was 2.3%. We recruited 130 (active arms) and 65 subjects (placebo arms), allowing for follow-up losses.

Randomization, allocation and blinding

Randomization was computer generated using a randomly permuted, variable block design, stratified by site, in a 2 active:1 placebo ratio. Study codes and sequentially numbered, sealed opaque envelopes containing the drug/placebo regimen were kept securely at each site.

Study drugs/placebos sufficient for the study duration were packaged into kits. After enrolment, the site pharmacists opened the envelopes and assigned the appropriate drug kits. The randomization number of the assigned drug kit was the subject study number and was used on the case record forms.

Active and placebo oseltamivir capsules (Tamiflu®, Roche, Switzerland) and zanamivir/placebo (zanamivir, zanamivir placebo) Rotadisks and Diskhalers [Relenza® Rotadisk, GlaxoSmithKline (GSK), USA] were identical in appearance and supplied by their manufacturers (zanamivir placebo contained the same lactose inhalation powder).

Study assessments

Potential subjects were screened by history, questionnaires, clinical examination, haematology, biochemistry, 12-lead ECGs, lung function and urine pregnancy tests. On study, assessments were conducted at different times over 16 weeks. Pregnancy tests were repeated at week 4, 8, 12 and 16. Women found to be pregnant were withdrawn from further study drug/placebo.

Subjects were asked how they were each time they received the study drug/placebo and grade 2 and above AEs were noted. At week 0 (baseline), 4, 8, 12 and 16, team members also administered a symptom questionnaire of 19 symptoms [cough, sore throat, difficulty breathing, wheeze, appetite, nausea, vomiting, abdominal pain, diarrhoea (>3 liquid stools/day), constipation, skin rash, itching, muscle pains, joint pains, headache, dizziness, visual hallucinations, auditory hallucinations, fatigue] and 'others.'

HADS was administered at week 0, 1, 2, 4, 8, 12 and 16 or if subjects withdrew from the study. Scores of 0–7 are normal, 8–10 borderline and ≥11 indicate anxiety or depression. The Thai Delirium Rating Scale (TDRS) was administered if indicated; a score >10 suggests acute confusion.

Blood sampling

Haematology and biochemistry were performed at week 0, 1, 2, 4, 8, 12 and 16. Samples for oseltamivir and OC drug measurements were taken at week 2 and 16 (trough concentrations), week 1, 4, 8 and 12 [peak concentrations (2–4 h post-dose)] and randomly for SAEs or grade 3 or 4 AEs possibly, probably or definitely related to oseltamivir.

Lung function and ECG

The FVC, FEV_1, FEV_1/FVC ratio and forced expiratory flow between 25% and 75% of the FVC (FEF25–75%) were recorded at week 0, 1, 4/5, 8/9 and 11/12 [Sensormedics Corporation, California, USA (Siriraj Hospital) and Micro Medical Ltd, UK (HTD)]. Twelve-lead ECGs were performed at week 0, 1, 8 and 16 [Nikon Kohden Corp., Japan (HTD)] and read by experienced team physicians assisted by cardiologists. We used the Fridericia corrected QT interval: $QTcF = QT/\sqrt[3]{}$ (RR interval).

ILI and virological diagnostics

Subjects with an ILI (oral temperature >37.8°C) and cough and/or sore throat/rhinorrhoea were clinically evaluated and had nasopharyngeal aspirate and throat swab samples taken for real-time reverse transcriptase PCR (RT–PCR) for seasonal influenza A/H1N1, A/H3N2, B and pdm09 A/H1N1;[43] acute and 14 day convalescent influenza serology (haemagglutination inhibition and microneutralization)[44] and oseltamivir/OC concentrations.

Viral culture was performed on Madin-Darby Canine Kidney (MDCK) cells ATCC CCL-34.[44] If influenza viruses were isolated, they were further tested by sequencing of haemagglutinin and neuraminidase genes for mutational positions of drug resistance, phenotypic testing (in-house viral nucleoprotein reduction assay against oseltamivir and zanamivir using MDCK cells) and neuraminidase inhibition assay to measure 50% inhibitory concentration (IC_{50}).[45] If subjects had RT–PCR-proven influenza, they were withdrawn from the study and treated as clinically indicated.

Statistical methods

Data management, undertaken by Biophics, Thailand, used the Datafax system. All analyses [Stata v11 (Stata Corporation, College Station, TX, USA)] were based on subjects who received at least one dose of study drug/placebo: (1) χ^2 or Fisher's exact test (proportional data); (2) comparisons between continuous variables at a given time and baseline were assessed by paired *t*-test or Wilcoxon signed-rank test; (3) changes in laboratory, lung function parameters and QTcF intervals over time by random effects regression model to account for multiple measurements per subject; and (4) linear changes in these parameters over time were examined and tested using likelihood ratio statistics.

Results

Patient disposition and general characteristics

Of the 451 screened subjects, 390 [285 (73.1%) females] were enrolled; 25 (6.4%) did not complete the study (Figure 1): 9 (oseltamivir), 3 (oseltamivir placebo), 10 (zanamivir) and 3 (zanamivir placebo). Five physician withdrawals were due to the late discovery of four wrongly randomized subjects [abnormal lung function (3), received an investigational drug (1)] and one subject who was not compliant with taking the study drug/placebo. Most volunteers were free of symptoms, signs and abnormal test results (Table 1). The study started in October 2009; the last patient finished follow-up in April 2010.

Compliance

A total of 12 741 oseltamivir/placebo tablets and 12 879 zanamivir/placebo inhalations were supervised; self-administered treatments were 8262 and 8189, respectively. Fully compliant subjects were similar ($P = 0.5$): 120/129 (93%, oseltamivir), 62/65 (95.4%, oseltamivir placebo), 118/131 (90.1%, zanamivir) and 62/65 (95.4%, zanamivir placebo); proportions taking ≥90 doses were 93.8%, 96.9%, 93.1% and 95.4%, respectively.

Outcomes

A total of 102 AEs, graded ≥2, were reported by or detected in 69/390 (17.7%) subjects (Table 2): oseltamivir, 29 AEs in 23/129 (17.8%) subjects; oseltamivir placebo, 25 in 15/65 (23.1%) subjects; zanamivir, 32 in 23/131 (17.6%) subjects; zanamivir placebo, 16 in 8/65 (12.3%) subjects ($P = 0.459$ in a four-arm comparison). All AEs, except one (see below), and all eight SAEs were classified by study physicians as unrelated or unlikely related to the study drugs.

Eighty-five (83.3%) AEs were grade 2. Twelve of the 17 grade 3–4 AEs required treatment: urinary calculus, dengue fever ($n = 2$), fall ($n = 2$), gastritis, head injury, joint injury, joint sprain, acute otitis media, urinary tract infection and a wound infection. The most frequently reported grade 2–4 AEs (Table 2) were coincident infections ($n = 22$) and fevers ($n = 4$) for frequencies of

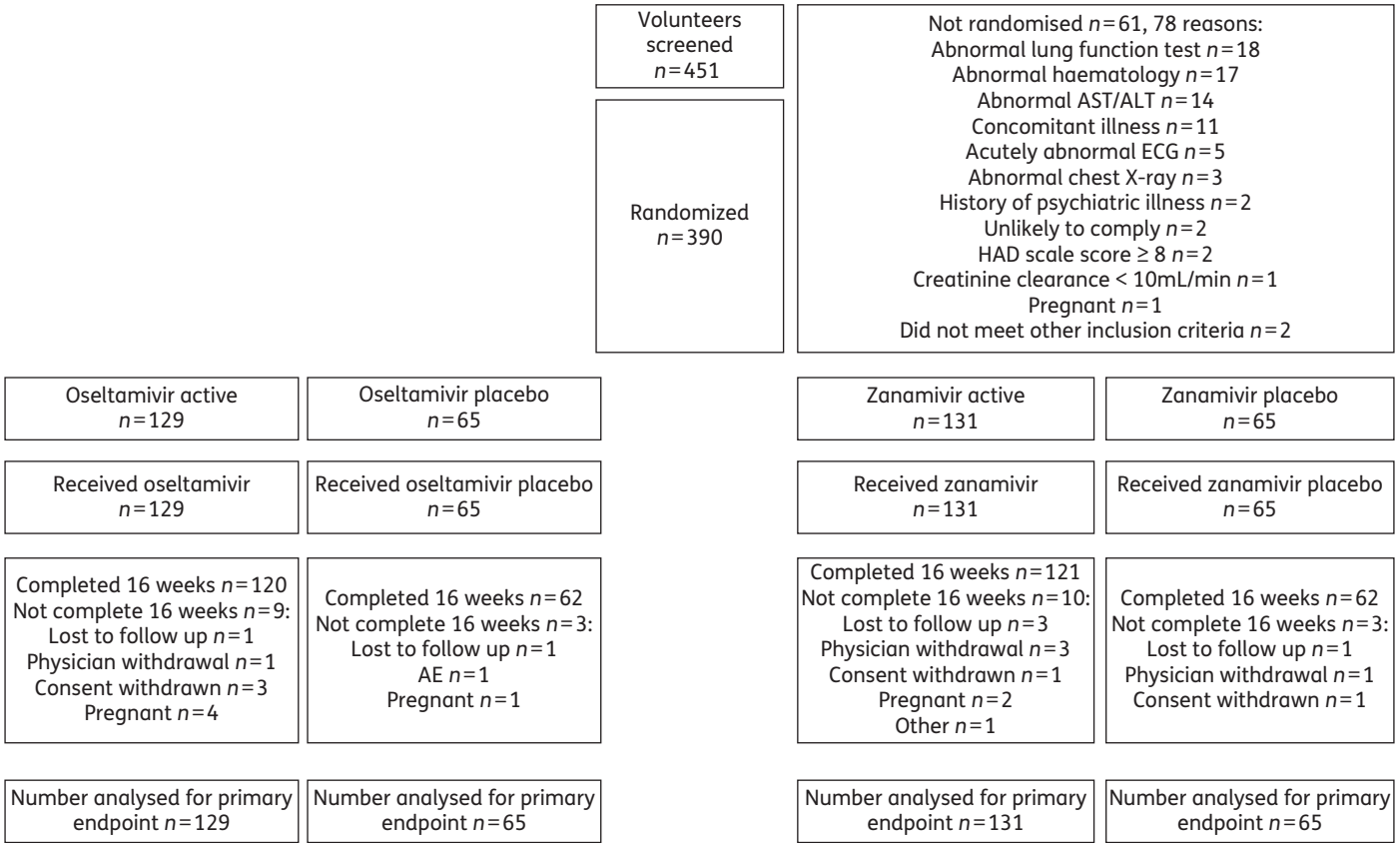

Figure 1. Trial profile.

25.5% (26/102 AEs) and 5.9% (23/390 subjects), abnormal biochemistry results [$n=25$, 24.5% and 5.4% (21/390)] and gastrointestinal (GI) symptoms [$n=18$, 17.6% and 3.8% (15/390)]. There were no significant differences ($P=0.2-1.0$) in clinical and laboratory AE rates between oseltamivir versus oseltamivir placebo and zanamivir versus zanamivir placebo. There were eight SAEs; all were due to intercurrent illnesses (Table 3).

One oseltamivir/placebo recipient was withdrawn from the study because of an increase in liver enzymes that, at the time, was considered probably drug related. This recipient had baseline AST and ALT values of 45 IU/L. After ~8 weeks of oseltamivir/placebo she developed a grade 2, asymptomatic increase in AST and ALT of 151 and 142 IU/L, respectively. Hepatitis A, B and C serologies were negative; a liver ultrasound showed only marked fatty liver infiltration. Her code revealed she was an oseltamivir placebo recipient. She probably had non-alcoholic hepatic steatosis.

Twenty-one subjects had abnormal laboratory values graded ≥2; 16 returned to normal by study end and 5 were reported at the last follow-up. ALT, AST and total bilirubin values ranged from 101 to 245, 106 to 165 IU/L and 1.61 to 2.35 mg/dL, respectively. Creatine phosphokinase (CPK) values in three subjects were 948, 2692 and 951 IU/L; all resolved within 1 week, but in the subject whose CPK was 951 IU/L, the CPK rose again to 4726 IU/L at the last follow-up. No laboratory AE was related to either oseltamivir or zanamivir.

Symptom trends

Trends in the symptoms reported by the questionnaire are shown in Figures 2–5. Most symptoms were grade 1; only five patients reported grade 2 symptoms. Changes in symptom frequencies between arms were not significantly different except for cough. At week 4, mild (grade 1) cough was significantly ($P=0.037$) higher in the zanamivir arm [10.3% (13/126)] versus the zanamivir placebo arm [1.6% (1/63)] and significantly ($P=0.045$) higher in the oseltamivir placebo arm [8.1% (5/62)] versus the oseltamivir arm [1.7% (2/121)] at week 16. Wheezing was not reported by any subject at any time.

HADS and TDRS scores

Most subjects had HADS scores <8 during the study. No subject had a score ≥11. Three [9 ($n=2$)] and four [9 ($n=1$)] subjects recorded scores of 8 or 9 for anxiety and depression, respectively, at least once during the study; one subject had simultaneous anxiety and depression scores of 9. No scores persisted by study end. Anxiety scores were one each for oseltamivir, zanamivir and zanamivir placebo; elevated depression scores were oseltamivir 4/129 versus oseltamivir placebo 0/65 ($P=0.30$) and zanamivir 1/131 versus zanamivir placebo 1/65 ($P=1$). No subjects had an acute psychiatric AE.

Table 1. Baseline characteristics of enrolled subjects

Parameter	Oseltamivir ($n=129$)	Oseltamivir placebo ($n=65$)	Zanamivir ($n=131$)	Zanamivir placebo ($n=65$)
Age	32 (20–55)	30 (20–57)	31 (20–61)	30 (21–52)
Female	94 (72.9)	45 (69.2)	99 (75.6)	47 (72.3)
Male	35 (27.1)	20 (30.8)	32 (24.4)	18 (27.7)
No symptoms reported				
general symptoms	129 (100)	65 (100)	129 (98.5)	64 (98.5)
respiratory symptoms	120 (93.0)	62 (95.4)	122 (93.1)	63 (96.9)
gastrointestinal symptoms	126 (97.7)	60 (92.3)	122 (93.1)	61 (93.8)
skin symptoms	127 (98.5)	64 (98.5)	130 (99.2)	65 (100)
musculoskeletal symptoms	115 (89.1)	57 (87.7)	121 (92.4)	58 (89.2)
neurological symptoms	126 (97.7)	62 (95.4)	126 (96.2)	64 (98.5)
psychiatric symptoms	129 (100)	65 (100)	131 (100)	65 (100)
Physical examination				
temperature (°C)	36.4 (36.0–37.3)	36.4 (35.9–37.2)	36.5 (36.0–37.3)	36.5 (36.0–37.3)
pulse (beats/min)	76 (60–104)	75 (50–99)	75 (50–98)	76 (58–98)
systolic BP (mmHg)	112 (95–147)	120 (90–142)	111 (90–144)	110 (89–141)
diastolic BP (mmHg)	70 (50–106)	70 (48–91)	70 (50–97)	70 (50–96)
respiratory rate/minute	18 (16–20)	18 (16–20)	18 (16–20)	20 (16–20)
GA: normal	124 (96.1)	64 (98.5)	126 (96.2)	60 (92.3)
ENT: normal	125 (96.9)	64 (98.5)	129 (98.5)	65 (100)
heart : normal	129 (100)	65 (100)	131 (100)	65 (100)
lungs: normal	129 (100)	65 (100)	131 (100)	65 (100)
abdomen: normal	128 (99.2)	64 (98.5)	129 (98.5)	61 (93.9)
neurological: normal	129 (100)	65 (100)	131 (100)	65 (100)
skin: normal	127 (98.5)	63 (96.9)	126 (96.2)	62 (95.4)
Pulmonary function tests				
FEV_1/FVC ratio: normal	128 (99.2)	63 (96.9)	128 (97.7)	63 (96.9)
grade 1	1 (0.8)	2 (3.1)	3 (2.3)	2 (3.1)
mean FEV_1/FVC[a]	87.1 (5.1)	86.4 (5.1)	86.4 (5.6)	86.2 (5.5)
HADS				
anxiety score 0–7	129 (100)	65 (100)	131 (100)	65 (100)
depression score 0–7	129 (100)	65 (100)	131 (100)	65 (100)
Haematology				
haemoglobin (g/dL)	12.8 (11–16.3)	13 (11.1–15.5)	12.7 (11–120)	13.1 (11.3–16.1)
platelet count ($10^3/\mu L$)	261 (141–483)	249 (134–390)	248 (135–434)	251 (135–370)
white blood cell ($10^3/\mu L$)	6.8 (3.4–10.6)	7.2 (3.9–10.5)	6.6 (3.9–13.0)	6.7 (3.5–10.7)
Biochemistry				
glucose (mg/dL)	91 (75–118)	90 (75–124)	91 (75–129)	91 (77–108)
creatinine (mg/dL)	0.7 (0.5–1.18)	0.75 (0.5–1.27)	0.74 (0.49–1.37)	0.75 (0.4–1.13)
total bilirubin (mg/dL)	0.48 (0.16–1.44)	0.52 (0.18–1.78)	0.49 (0.04–1.62)	0.49 (0.09–0.95)
AST (IU/L)	20 (11–44)	19 (14–45)	19 (8–40)	20 (12–45)
ALT (IU/L)	16 (5–58)	16 (9–50)	15 (6–51)	16 (7–57)
sodium (mmol/L)	140 (136–144)	140 (136–146)	140 (135–145)	140 (136–147)
potassium (mmol/L)	4.1 (3.49–5.3)	4.2 (3.39–5.15)	4.1 (3.4–4.9)	4.14 (3.4–5.34)
CPK (IU/L)	104 (44–800)	108 (7.9–1,015)	100 (32–504)	112 (51–335)

All continuous data are the median (range) unless otherwise stated. Proportional data are number (%).
BP, blood pressure; GA, general assessment; ENT, ears nose and throat; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; HADS, Hospital Anxiety Depression Scale; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine phosphokinase.
[a]Values are the mean (standard deviation).

Table 2. Summary of the 102 reported and detected grade ≥2 clinical and laboratory AEs, classified by the System Organ Classification

	Oseltamivir (*n*=129)	Oseltamivir placebo (*n*=65)	Zanamivir (*n*=131)	Zanamivir placebo (*n*=65)
Number of subjects with at least one AE	23 (17.8%)	15 (23.1%)	23 (17.6%)	8 (12.3%)
Number of AEs (total)	29	25	32	16
Blood and lymphatic system disorders (total)	1	0	0	1
thrombocytopenia	1 (3.4)[a]	0	0	1 (6.3)
Cardiac disorders (total)	1	0	0	0
tachycardia	1 (3.4)	0	0	0
Gastrointestinal disorders (total)	6	5	5	2
abdominal pain	0	1 (4.0)	0	0
diarrhoea	0	1 (4.0)	0	2 (12.5)
dyspepsia	0	0	1 (3.1)	0
enteritis	0	1 (4.0)	0	0
food poisoning	0	1 (4.0)	0	0
gastritis	1 (3.4)	0	2 (6.3)[b]	0
gastroenteritis	3 (10.3)	0	2 (6.3)	0
nausea	0	1 (4.0)	0	0
vomiting	2 (6.9)	0	0	0
General disorders and administration site conditions (total)	0	2	2	0
influenza-like illness	0	1 (4.0)	2 (6.3)	0
pyrexia	0	1 (4.0)	0	0
Infections and infestations (total)	5	6	7	4
adenoviral conjunctivitis	1 (3.4)	0	0	0
conjunctivitis viral	1 (3.4)	0	0	0
dengue fever	0	0	2 (6.3)	0
hordeolum	0	1 (4.0)	0	0
otitis media acute	0	0	1 (3.1)	0
pharyngitis	2 (6.9)	0	0	0
rhinitis	0	1 (4.0)	0	0
skin infection	0	0	1 (3.1)	0
upper respiratory tract infection	0	2 (8.0)	1 (3.1)	3 (18.8)
urinary tract infection	1 (3.4)	0	0	0
varicella	0	1 (4.0)	0	0
viral infection	0	1 (4.0)	0	0
viral pharyngitis	0	0	2 (6.3)	0
viral upper respiratory tract infection	0	0	0	1 (6.3)
Injury, poisoning and procedural complications (total)	2	2	7	0
fall	0	0	2 (6.3)	0
head injury	0	0	1 (3.1)	0
joint injury	0	1 (4.0)	0	0
joint sprain	0	1 (4.0)	0	0
laceration	0	0	3 (9.4)	0
wound	2 (6.9)	0	0	0
wrist fracture	0	0	1 (3.1)	0
Investigations (total)	7	6	5	4
ALT increased	1 (3.5)	1 (4.0)	2 (6.3)	0
AST increased	0	2 (8.0)	1 (3.1)	1 (6.3)
bilirubin increased	3 (10.3)	1 (4.0)	2 (6.3)	2 (12.5)
CPK increased	1 (3.5)	2 (4.0)	0	1 (6.3)
pulmonary function test abnormal	2 (6.9)	0	0	0

Continued

Table 2. *Continued*

	Oseltamivir ($n=129$)	Oseltamivir placebo ($n=65$)	Zanamivir ($n=131$)	Zanamivir placebo ($n=65$)
Metabolism and nutrition disorders (total)	2	0	3	0
dyslipidaemia	0	0	1 (3.1)	0
hyperglycaemia	2 (6.9)	0	2 (3.1)	0
Musculoskeletal and connective tissue disorders (total)	1	1	2	0
back pain	0	1 (4.0)	1 (3.1)	0
myalgia	1 (3.4)	0	1 (3.1)	0
Nervous system disorders (total)	2	0	0	3
headache	1 (3.4)	0	0	1 (6.3)
tension headache	0	0	0	2 (12.5)
vertigo	1 (3.4)	0	0	0
Pregnancy, puerperium and perinatal conditions (total)	1	1	1	0
abortion complete	0	0	1 (3.1)	0
abortion complete complicated	0	1 (4.0)	0	0
blighted ovum	1 (3.4)	0	0	0
Psychiatric disorders (total)	0	2	0	0
anxiety	0	1 (4.0)	0	0
stress	0	1 (4.0)	0	0
Renal and urinary disorders (total)	0	0	0	1
calculus urinary	0	0	0	1 (6.3)
Vascular disorders (total)	1	0	0	0
hypertension	1 (3.4)	0	0	0

[a]Value shown is the number with the percentage of the total number of AEs for that arm in parentheses.
[b]One patient complained originally of dyspnea, but on further evaluation was diagnosed with gastritis.

Table 3. Summary of SAEs

	Oseltamivir ($n=129$)	Oseltamivir placebo ($n=65$)	Zanamivir ($n=131$)	Zanamivir placebo ($n=65$)
Number (%) of SAEs	2 (1.6)	2 (3.1)	4 (3.1)	0 (0)
Gastrointestinal disorders				
gastritis	0	0	1	0
infections and infestations				
otitis media acute	0	0	1	0
urinary tract infection	1	0	0	0
Injury, poisoning and procedural complications				
fall	0	0	1	0
joint injury	0	1	0	0
Pregnancy, puerperium and perinatal conditions				
abortion complete	0	0	1	0
abortion complete complicated	0	1	0	0
blighted ovum	1	0	0	0

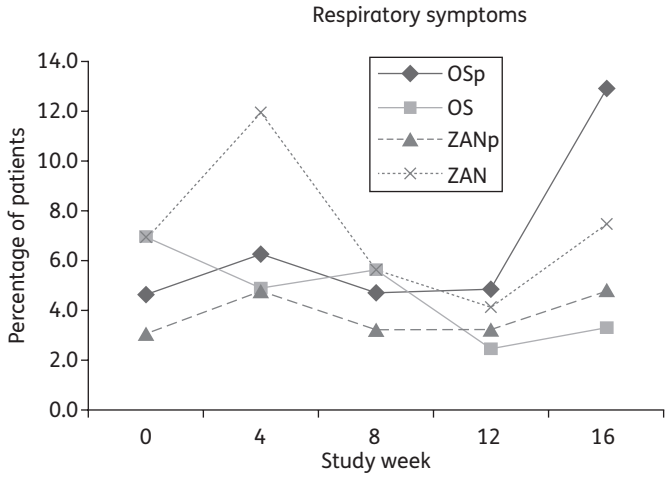

Figure 2. Trends in respiratory symptoms by study week elicited by questionnaire for oseltamivir (OS)/placebo (OSp) and zanamivir (ZAN)/placebo (ZANp), expressed as subject proportions.

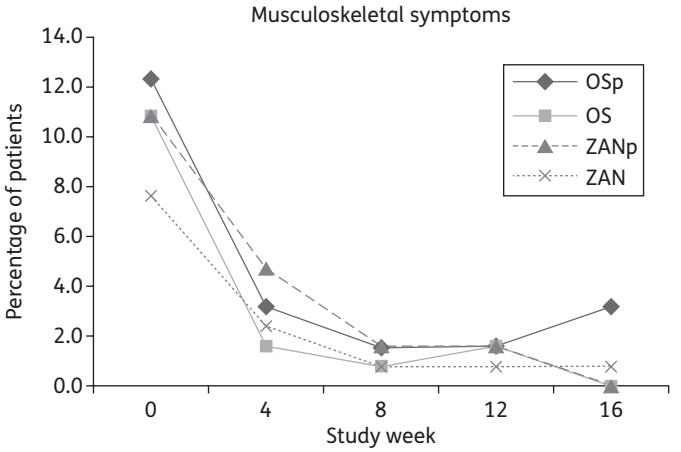

Figure 4. Trends in musculoskeletal symptoms by study week elicited by questionnaire for oseltamivir (OS)/placebo (OSp) and zanamivir (ZAN)/placebo (ZANp), expressed as subject proportions.

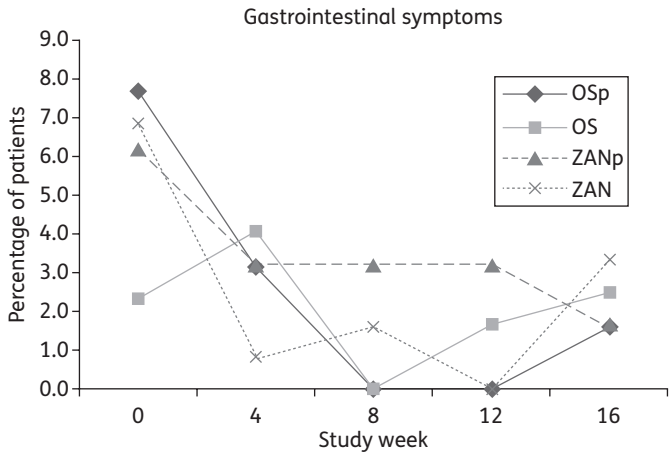

Figure 3. Trends in gastrointestinal symptoms by study week elicited by questionnaire for oseltamivir (OS)/placebo (OSp) and zanamivir (ZAN)/placebo (ZANp), expressed as subject proportions.

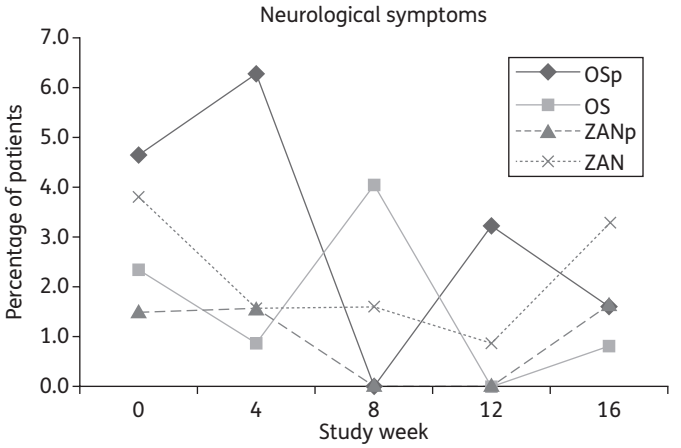

Figure 5. Trends in neurological symptoms by study week elicited by questionnaire for oseltamivir (OS)/placebo (OSp) and zanamivir (ZAN)/placebo (ZANp), expressed as subject proportions.

Lung function and ECGs

The mean FEV_1/FVC ratios over time were very similar in the four arms at baseline and subsequent follow-ups (data not shown). By study end the FEV_1/FVC ratio for all subjects increased significantly ($P<0.001$ versus day 0) by a mean of 1.8% (95% CI 1.3–2.3%) with similar changes between each arm.

No subject had a QTcF $\geq$500 ms nor an increase from baseline >25% at any timepoint. Twenty-three subjects had a QTcF increase $\geq$30 ms from baseline, distributed similarly ($P=1$) between the arms: 8/129 (6.2%, oseltamivir), 4/65 (6.15%, oseltamivir placebo), 8/131 (6.1%, zanamivir) and 3/65 (4.6%, zanamivir placebo).

Influenza-like illness

Six subjects (1.5%) had ILIs: oseltamivir placebo=2, zanamivir =3 and zanamivir placebo=1. None was RT–PCR confirmed for influenza A or B, so no further virological investigations were done. Two ILI subjects had acute dengue fever and exudative tonsillitis.

Pregnancies

Eight women became pregnant during the study. The length of exposure to study drugs/placebos at the time the pregnancies were detected varied from 7 to 112 days. Four delivered healthy female babies (oseltamivir exposure 7, 28 and 82 days;

zanamivir 16 days), two had spontaneous abortions (zanamivir 84 days; oseltamivir placebo 20 days), one had a blighted ovum (oseltamivir 112 days) and one was lost to follow-up (zanamivir 28 days).

Discussion

In this 16 week study, we showed that healthy Thai health professionals tolerated well oral oseltamivir or zanamivir inhalations. No volunteer stopped oseltamivir or zanamivir because of an adverse drug reaction.

Subjects were followed up closely, ensuring high drug adherence and the early detection of AEs. We recorded clinical and laboratory AEs of at least moderate severity, as these were more likely to be clinically important. Accordingly, our AE rates were considerably lower compared with other studies of oseltamivir[30] and zanamivir[39] and were mostly due to intercurrent illnesses, transient increases in biochemistry and GI symptoms. During the study the clinicians judged that one AE was study drug/placebo related but, on analysis, the subject had received oseltamivir placebo; her diagnosis was probably non-alcoholic hepatic steatosis. Mild cough was reported significantly most often in the zanamivir arm at week 4, declining thereafter, and in the oseltamivir placebo group at study end. Both might be chance findings, but we cannot exclude definitively that zanamivir may cause a transient cough when first used.

The changes in lung function in our lung healthy subjects were clinically unremarkable (more analyses will be presented elsewhere). Similarly there were no clinically significant changes in QTcF intervals, consistent with previous work.[46,47]

Our study had limitations. Both drugs were administered following their current regulatory labels. Pregnant women were excluded. This vulnerable group, which suffers high influenza-related mortality, especially in the third trimester,[48,49] is a target group for vaccination rather than prophylaxis.[50] This has implications for policy regarding pregnant nurses, who understand the risks to health of contracting influenza at work and the unknown risks of chemoprophylaxis as important concerns.[51]

Although women of child-bearing age agreed to use contraception to be enrolled, eight (just under 3%) became pregnant; this remains unexplained. There were no congenital abnormalities in the four live births, three and one of whom had been exposed to oseltamivir and zanamivir, respectively. Although these small numbers *per se* tell us little regarding the safety of both drugs, they are useful contributors to a pregnancy register of drug exposure. Limited data suggest oseltamivir exposure in pregnancy may not be associated with adverse outcomes for the mother and foetus.[52,53] Currently, there is no pregnancy exposure register for zanamivir. More data collection on accidental exposure to both drugs in early pregnancy are needed.

We also excluded subjects with moderate/severe obstructive airways disease because inhaled zanamivir has been associated rarely with increases in airways obstruction, even in individuals without pre-existing airways disease.[54] Although inhaled zanamivir use in asthmatics and COPD sufferers is not an absolute contraindication, it is not recommended; thus, oseltamivir is the preferred choice. These exclusions and others mandated by the protocol (e.g. laboratory abnormalities) limit the generalizability of our findings to predominantly healthy subjects.

The study was not powered to detect rare side effects of either drug, notably acute psychiatric reactions or acute bronchospasm. Although thought initially to be oseltamivir related, the acute psychiatric reactions are probably influenza related,[36] with limited data suggesting a protective effect in oseltamivir-treated influenza patients.[38]

We investigated six subjects with symptomatic ILI, but none had influenza. The study period (October 2009–April 2010) occurred between the two peaks of influenza activity, when community influenza transmission was low.[55] However, prophylaxis failure has also been associated with asymptomatic influenza, and we cannot exclude this possibility.[56] This may be important for infection control in the hospital environment and is an area of future research.

To conclude, this study demonstrated good tolerability of supervised oseltamivir and inhaled zanamivir for 16 weeks. Both are options for influenza prophylaxis. Further work on the effectiveness and acceptability of unsupervised, long-term prophylaxis is warranted.

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Transparency declarations

None to declare.

Author contributions

Study PI, T. A.; PI of HTM site, S. P.; protocol development, W. R. J. T., T. A., N. D., C. F., N. J. W. and K. S.; data analysis, K. S. and P. S.; first draft of the article, W. R. J. T., K. S. and A. T.; clinical team, T. A., S. P., W. R., P. J., W. T., S. S. and P. W.; virology, P. P.; pharmacokinetics, N. L. and J. T.; study coordination, C. F. and W. R. J. T.; and access to data and data guarantor, K. S.

References

1 Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. *Emerg Infect Dis* 2006; **12**: 15–22.

2 Cauchemez S, Ferguson NM, Wachtel C *et al*. Closure of schools during an influenza pandemic. *Lancet Infect Dis* 2009; **9**: 473–81.

3 Barr IG, Hurt AC, Iannello P *et al*. Increased adamantane resistance in influenza A(H3) viruses in Australia and neighbouring countries in 2005. *Antiviral Res* 2007; **73**: 112–7.

4 Bai GR, Chittaganpitch M, Kanai Y *et al*. Amantadine- and oseltamivir-resistant variants of influenza A viruses in Thailand. *Biochem Biophys Res Commun* 2009; **390**: 897–901.

5 Hurt AC, Selleck P, Komadina N *et al*. Susceptibility of highly pathogenic A(H5N1) avian influenza viruses to the neuraminidase inhibitors and adamantanes. *Antiviral Res* 2007; **73**: 228–31.

6 Drinka PJ, Haupt T. Emergence of rimantadine-resistant virus within 6 days of starting rimantadine prophylaxis with oseltamivir treatment of symptomatic cases. *J Am Geriatr Soc* 2007; **55**: 923–6.

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

8 Hayden FG, Atmar RL, Schilling M *et al*. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999; **341**: 1336–43.

9 LaForce C, Man CY, Henderson FW *et al*. Efficacy and safety of inhaled zanamivir in the prevention of influenza in community-dwelling, high-risk adult and adolescent subjects: a 28-day, multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther* 2007; **29**: 1579–90; discussion 7–8.

10 Kashiwagi S, Kudoh S, Watanabe A *et al*. [Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza—placebo-controlled double-blind multicenter phase III trial]. *Kansenshogaku Zasshi* 2000; **74**: 1062–76.

11 Monto AS, Robinson DP, Herlocher ML *et al*. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 1999; **282**: 31–5.

12 Lee VJ, Yap J, Cook AR *et al*. Oseltamivir ring prophylaxis for containment of 2009 H1N1 influenza outbreaks. *N Engl J Med* 2010; **362**: 2166–74.

13 Monto AS, Pichichero ME, Blanckenberg SJ *et al*. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis* 2002; **186**: 1582–8.

14 Hayden FG, Gubareva LV, Monto AS *et al*. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. *N Engl J Med* 2000; **343**: 1282–9.

15 Jefferson T, Jones M, Doshi P *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev* 2010; **issue 2**: CD001265.

16 Jackson RJ, Cooper KL, Tappenden P *et al*. Oseltamivir, zanamivir and amantadine in the prevention of influenza: a systematic review. *J Infect* 2011; **62**: 14–25.

17 Hurt AC, Deng YM, Ernest J *et al*. Oseltamivir-resistant influenza viruses circulating during the first year of the influenza A(H1N1) 2009 pandemic in the Asia-Pacific region, March 2009 to March 2010. *Euro Surveill* 2011; **16**: pii=19770.

18 McKimm-Breschkin JL, Selleck PW, Usman TB *et al*. Reduced sensitivity of influenza A (H5N1) to oseltamivir. *Emerg Infect Dis* 2007; **13**: 1354–7.

19 Okomo-Adhiambo M, Sleeman K, Ballenger K *et al*. Neuraminidase inhibitor susceptibility testing in human influenza viruses: a laboratory surveillance perspective. *Viruses* 2010; **2**: 2269–89.

20 Hurt AC, Ernest J, Deng YM *et al*. Emergence and spread of oseltamivir-resistant A(H1N1) influenza viruses in Oceania, South East Asia and South Africa. *Antiviral Res* 2009; **83**: 90–3.

21 Meijer A, Lackenby A, Hungnes O *et al*. Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007–08 season. *Emerg Infect Dis* 2009; **15**: 552–60.

22 Ciancio BC, Meerhoff TJ, Kramarz P *et al*. Oseltamivir-resistant influenza A(H1N1) viruses detected in Europe during season 2007–8 had epidemiologic and clinical characteristics similar to co-circulating susceptible A(H1N1) viruses. *Euro Surveill* 2009; **14**: pii=19412.

23 WHO Flu net. http://gamapserver.who.int/gareports/Default.aspx?ReportNo=6 (1 September 2012, date last accessed).

24 Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis—North Carolina, 2009. *MMWR Morb Mortal Wkly Rep* 2009; **58**: 969–72.

25 Baz M, Abed Y, Papenburg J *et al*. Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. *N Engl J Med* 2009; **361**: 2296–7.

26 de Jong MD, Tran TT, Truong HK *et al*. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; **353**: 2667–72.

27 Hurt A, Lee R, Leang S *et al*. Increased detection in Australia and Singapore of a novel influenza A(H1N1)2009 variant with reduced oseltamivir and zanamivir sensitivity due to a S247N neuraminidase mutation. *Euro Surveill* 2011; **16**: pii=19884.

28 Hurt AC, Holien JK, Parker M *et al*. Zanamivir-resistant influenza viruses with a novel neuraminidase mutation. *J Virol* 2009; **83**: 10366–73.

29 Reisinger K, Shu D, Cupelli L *et al*. Safety and tolerability of a 6-week course of oseltamivir prophylaxis for seasonal influenza in children. *Influenza Other Respir Viruses* 2012; doi 10.1111/j.1750-2659.2012.00367.x.

30 Dutkowski R, Thakrar B, Froehlich E *et al*. Safety and pharmacology of oseltamivir in clinical use. *Drug Saf* 2003; **26**: 787–801.

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

32 Strong M, Burrows J, Stedman E *et al*. Adverse drug effects following oseltamivir mass treatment and prophylaxis in a school outbreak of 2009 pandemic influenza A(H1N1) in June 2009, Sheffield, United Kingdom. *Euro Surveill* 2010; **15**: pii=19565.

33 Coleman BL, Boggild AK, Drews SJ *et al*. Respiratory illnesses in Canadian health care workers: a pilot study of influenza vaccine and oseltamivir prophylaxis during the 2007/2008 influenza season. *Influenza Other Respir Viruses* 2011; **5**: 404–8.

34 Okumura A, Nakano T, Fukumoto Y *et al*. Delirious behavior in children with influenza: its clinical features and EEG findings. *Brain Dev* 2005; **27**: 271–4.

35 Okumura A, Kubota T, Kato T *et al*. Oseltamivir and delirious behavior in children with influenza. *Pediatr Infect Dis J* 2006; **25**: 572.

36 Toovey S, Rayner C, Prinssen E *et al*. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Saf* 2008; **31**: 1097–114.

37 Blumentals WA, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. *Med Gen Med* 2007; **9**: 23.

38 Casscells SW, Granger E, Kress AM *et al*. The association between oseltamivir use and adverse neuropsychiatric outcomes among TRICARE

beneficiaries, ages 1 through 21 years diagnosed with influenza. *Int J Adolesc Med Health* 2009; **21**: 79–89.

39 Glaxo Smith Kline 2011. Package insert for Relenza. http://us.gsk.com/products/assets/us_relenza.pdf (1 September 2012, date last accessed).

40 Freund B, Gravenstein S, Elliott M *et al*. Zanamivir: a review of clinical safety. *Drug Saf* 1999; **21**: 267–81.

41 Gravenstein S, Johnston SL, Loeschel E *et al*. Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Saf* 2001; **24**: 1113–25.

42 Division of AIDS table for grading the severity of adult and pediatric adverse events 2004. http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/daidsaegradingtable.pdf (1 January 2012, date last accessed).

43 WHO 2009. CDC protocol of realtime RTPCR for influenza A (H1N1). http://www.who.int/csr/resources/publications/swineflu/realtimeptpcr/en/index.html (1 January 2012, date last accessed).

44 World Health Organization, *Department of Epidemic and Pandemic Alert and Response*. WHO Manual on Animal Influenza Diagnosis and Surveillance. Geneva: World Health Organization; 2002.

45 Wetherall NT, Trivedi T, Zeller J *et al*. Evaluation of neuraminidase enzyme assays using different substrates to measure susceptibility of influenza virus clinical isolates to neuraminidase inhibitors: report of the neuraminidase inhibitor susceptibility network. *J Clin Microbiol* 2003; **41**: 742–50.

46 Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. *Int J Antimicrob Agents* 2010; **35**: 461–7.

47 A phase I, randomized, placebo-controlled, four-way crossover study to evaluate the effect of intravenous (IV) zanamivir on cardiac conduction as assessed by 12-lead electrocardiogram (ECG) with moxifloxacin as a positive control in healthy volunteers. http://www.gsk-clinicalstudyregister.com/quick-search-list.jsp?tab=results&letterrange=All&type=GSK+Study+ID& item=114346&studyType= All& phase=All&status=All&population=All&marketing= All &country=All& studyId=114346 (2 May 2012, date last accessed).

48 Dubar G, Azria E, Tesniere A *et al*. French experience of 2009 A/H1N1v influenza in pregnant women. *PLoS One* 2010; **5**: pii=e13112.

49 Jamieson DJ, Honein MA, Rasmussen SA *et al*. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009; **374**: 451–8.

50 2009 pandemic influenza A (H1N1) in pregnant women requiring intensive care—New York City, 2009. *MMWR Morb Mortal Wkly Rep* 2009; **59**: 321–6.

51 Phillips KP, O'Sullivan TL, Dow D *et al*. Infectious respiratory disease outbreaks and pregnancy: occupational health and safety concerns of Canadian nurses. *Prehosp Disaster Med* 2011; **26**: 114–21.

52 Donner B, Niranjan V, Hoffmann G. Safety of oseltamivir in pregnancy: a review of preclinical and clinical data. *Drug Saf* 2010; **33**: 631–42.

53 Tanaka T, Nakajima K, Murashima A *et al*. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. *CMAJ* 2009; **181**: 55–8.

54 Eiland LS, Eiland EH. Zanamivir for the prevention of influenza in adults and children age 5 years and older. *Ther Clin Risk Manag* 2007; **3**: 461–5.

55 Ungchusak K, Sawanpanyalert P, Hanchoworakul W *et al*. Lessons learned from influenza A(H1N1)pdm09 pandemic response in Thailand. *Emerg Infect Dis* 2012; **18**: 1058–64.

56 Lee VJ, Yap J, Maurer-Stroh S *et al*. Investigation of causes of oseltamivir chemoprophylaxis failures during influenza A (H1N1–2009) outbreaks. *J Clin Virol* 2011; **50**: 104–8.