Background: The neuraminidase inhibitors are the treatment of choice for influenza virus infection. Oseltamivir-resistant (OsR) strains of influenza A(H1N1)pdm09 are described, but the effect of higher dose oseltamivir on efficacy, safety and emergence of resistance has not been addressed in the developed setting in outpatients. The objectives of the study were to compare standard dose (SD) versus double dose (DD) oseltamivir regimens for frequency of detecting OsR influenza virus, clinical disease resolution, virological clearance and adverse events. 

Methods: This was an unblinded randomized controlled trial of community-based patients with confirmed influenza. Participants were randomized to a 5-day regimen of either SD or DD oseltamivir.

Results: Of 52 participants (aged 4.8–54.8 years), 25 received SD and 27 DD oseltamivir. Clinical resolution did not differ by dosing regimen ($P=0.43$); neither did virological clearance differ for either influenza A ($P=0.20$) or B ($P=0.70$). Adverse events, predominantly gastrointestinal, were greater with DD than SD ($P=0.04$). One OsR strain was detected prior to treatment and two individuals developed OsR strains during treatment, one each on SD and DD. Those with OsR strains did not appear to have a different clinical course.

Conclusions: DD oseltamivir did not appear to provide a clinical or virological advantage, nor reduce the emergence of oseltamivir resistance, but our study was underpowered. Adverse events occurred more frequently on DD compared to SD oseltamivir.

Introduction

Neuraminidase inhibitors (NAIs; for example, oseltamivir and zanamivir) are the treatment of choice against seasonal influenza. Since NAIs were introduced in 1999 and until 2007, ≤1% of viruses tested had mutations conferring oseltamivir resistance [1,2]. Oseltamivir-resistant (OsR) influenza A/H1N1 was first detected in Europe during the northern hemisphere winter of 2007–2008 and spread globally, such that by the 2008–2009 northern hemisphere winter, most strains of seasonal influenza A/H1N1 were OsR [3–6]. No difference in clinical severity was noted between the OsR and oseltamivir-sensitive (OsS) viruses [7]. Influenza A(H1N1)pdm09 was first detected in Mexico in March 2009, with the World Health Organization (WHO) declaring a pandemic on 11 June 2009 [8]. Surveillance has detected an increasing minority of influenza A(H1N1)pdm09 viruses to be OsR, almost all bearing the H273Y mutation in the neuraminidase (NA) gene. Between 2009–2011 approximately 600 of >30,000 influenza A(H1N1)pdm09 viruses were reported by the WHO as OsR [9–11]. Both the circulating influenza A/H3N2 and influenza B strains have generally remained OsS.

In preparation for an influenza pandemic many nations stockpiled oseltamivir, preferring it to zanamivir for its oral administration, systemic bioavailability and licensure for use from ≥1 year of age, as opposed to ≥5 years with zanamivir. Filled oseltamivir prescriptions in Australia increased from approximately 25,000 in 2008 to more than 350,000 in 2009, a process that may potentially promote the emergence of OsR viruses [6].

NAIs bind to the surface protein NA of the influenza virus, preventing release of viral progeny from host cells. Oseltamivir may select drug-resistant strains of influenza, especially in the immunocompromised, in
whom there is reduced viral clearance and prolonged viral replication [12–15]. The most common resistance mutation for oseltamivir is an amino acid tyrosine substituting histidine (H275Y) in the NA gene, altering the NA1 binding site. This results in high-level resistance to oseltamivir but not zanamivir [16,17]. In clinical trials, OsR pre-pandemic influenza virus strains developed more frequently in children (5–27%) than in adults (1–2%) [18–23].

Higher doses of oseltamivir may more rapidly reduce viral load, averting the selection of resistant strains, but evidence of this is lacking. Double dose (DD) regimens of oseltamivir have been used in both immunocompromised and artificially ventilated patients [6,24,25]. This study aimed to investigate whether this would be an effective strategy to reduce oseltamivir resistance, particularly amongst children (≤15 years), recruited from both the children’s hospital and a general practice.

The objectives of this study were to investigate the effectiveness of DD (150 mg twice daily for adults or 10 mg/kg for children) compared with standard dose (SD; 75 mg twice daily or 5 mg/kg for children) oseltamivir in subjects ≥5 years old on the frequency of detection of OsR virus, clinical disease and adverse events (AEs).

Methods

Trial design
This was an unblinded, randomized, parallel 1:1 study.

Participants
Participants were those aged ≥5 years old, presenting within 48 h with fever ≥37.8°C, with at least one respiratory symptom and a positive QuickVue point-of-care test (POCT; Quidel, San Diego, CA, USA), for influenza A or B presenting to either a family practice or a children’s hospital emergency department in West Sydney [26,27]. Given the higher false-negative rate of rapid POCT in older children and adults compared to younger children, a rapid nucleic acid test (NAT) using PCR was implemented for POCT-negative cases: the GenXpert FLU assay (Cepheid, Sunnyvale, CA, USA), with results available within 4 h [28–30]. Those positive for either test were offered inclusion in the study.

Those excluded were patients with a secondary bacterial infection, a poorly controlled underlying medical condition as determined by the treating doctor, immunosuppression (for example, malignancy, transplant or immunosuppressive agents), pregnant or lactating females, known oseltamivir allergy, participation in another clinical trial with an investigational drug or device, or insufficient English language skills to give informed consent.

Interventions
Participants were randomized in equal numbers to either SD or DD of oseltamivir for 5 days. The study did not prescribe clinical management beyond oseltamivir.

Doses were as follows, and standard dosing adhered to international guidelines for children (≤15 years; Table 1) [31]. Adult SD (>15 years) was 75 mg twice daily and DD 150 mg twice daily.

Outcomes
The end points of this study were the difference in the percentage of OsR influenza viruses in patients treated with SD versus DD oseltamivir at day 5 of follow-up, rates of clinical resolution and of the shedding of influenza virus at day 5 ±1 and adverse event profiles between dosing regimens. Clinical resolution was determined by patient or caregiver nominating date of cessation of all originally reported symptoms.

Adverse events
AEs were defined as symptoms developing during therapy that were not present at baseline or a symptom as reported on the subject daily record as present at baseline which resolved for one or more days but subsequently reappeared during therapy.

Sample size
Allowing for a 20% drop-out rate, the original target was 125 patients, yielding 100 completed subjects, conferring an 80% probability of detecting a difference in the frequency of OsR virus emergence from 25% to 5% under a single-tailed test with α=0.05, based on a 2009 study of OsR emergence in 27% of children treated with oseltamivir for influenza A H1N1 [23].

Randomization and sequence generation
We used block randomization to allocate interventions. A colleague not involved in the trial used the Excel random number generator to generate the allocation sequence consisting of randomly permuted blocks of four. Randomization was unblinded to patients and clinicians but blinded to laboratory researchers.

Implementation
The study was carried out at The Children’s Hospital at Westmead and at a nearby general practice, during the Southern hemisphere winter 2011.

First visit (day 1)
The procedures at the first visit (the initial clinical presentation) included collecting nose and throat specimens using a flocked cotton swab, with performance of a rapid POCT and a rapid NAT if POCT was negative (instituted 12 July 2011, one-third of the way through recruitment to increase sensitivity) and dispensing...
oseltamivir. Study personnel completed a Baseline Clinical Symptoms Questionnaire for each subject, eliciting either presence or absence of temperature ≥37.8°C, sore throat, runny nose, shortness of breath, conjunctivitis, wheezing, diarrhoea, nausea, vomiting, myalgia, joint pain, headache, seizures, insomnia and dizziness. A urine pregnancy test was performed for females aged ≥9 years.

Second visit (day 5 ±1)
At follow-up, repeat swabs were collected. A day 5 Clinical Symptoms and Adverse Events questionnaire was completed.

Laboratory methods
All swabs were cultured on Madin–Darby canine kidney (MDCK) cells using shell vials and confirmed by immunofluorescence (influenza A and B DFA reagents; Diagnostic Hybrids, Athens, OH, USA). An in-house reverse transcriptase (RT)-PCR for influenza A matrix (M) gene and B nucleoprotein (NP) gene was also performed on the swabs. A rolling-circle amplification method confirmed the presence of the H275Y resistance mutation [32]. All isolates were sent to the WHO Collaborating Centre for Reference and Research on Influenza (WHOCC) in Melbourne, Victoria, Australia for ascertainment of influenza A subtype, resistance phenotype and genotype.

Statistical methods
Data were analysed according to a pre-specified plan, by intention-to-treat, using SPSS version 20 (2011, IBM, New York, NY, USA) for statistical analysis. Comparisons between treatment groups, and recruitment sites, for a significant difference (P<0.05) in baseline demographics, virological outcomes and AEs were performed by a two-sample t-test for continuous data with normal distribution, Wilcoxon’s rank sum test for continuous variables with non-normal distribution and a two-sample χ² test for binomial data. A Kaplan–Meier analysis was used to estimate ‘mean time to recovery’ (in days) and its corresponding 95% CI, for selected subgroups of the cohort. The Mantel Cox ‘log rank’ test was used to compare ‘mean times to recovery’ for different cohort sub-groups at the level of P<0.05.

Ethics
The Sydney Children’s Hospitals Network Human Research Ethics Committee approved the study. All patients or caregivers (for subjects aged <18 years) signed informed consent forms.

Results

Recruitment
A total of 52 participants were recruited over the 2011 influenza season April to August 2011 (Figure 1). Two patients, both in the standard dose group, had short hospital admissions; the rest were outpatients.

Baseline data
Neither age nor gender differed between the two treatment groups, with 62% of recruits being children (≤15 years). The general practice site recruited 20 adults (13 female) and 15 children (6 male); the Children’s Hospital recruited 17 children (4 female; Table 2). Almost all participants were healthy amongst the SD group, one child had uncomplicated, stable sickle cell anaemia and one adult had well-controlled epilepsy. In the DD group, one child had a treated Wolff–Parkinson–White syndrome, one child had a stable neurological condition with an unspecified myopathy and autism, one child had episodes of syncope that were under investigation but, inter-episodically, was neurologically normal.

Of the 50 cases for which an influenza type was determined by POCT or NAT, 21 (42%) had influenza A and 29 (58%) influenza B. Of the influenza A cases, 4 (19%, all adults) had A/H3N2 subtype (Table 3).

Outcomes

Clinical resolution
Outcomes for all 52 patients were analysed by intention-to-treat. There was no significant difference in time to clinical resolution between the two dosing regimens (Figures 2 and 3). A total of 8 of 25 (32%) on SD and 6 of 27 (22%) on DD oseltamivir had residual symptoms by treatment day 5 (P=0.43). Children recovered an average of one day faster than persons aged >15 years; this difference was significant comparing within the SD regimen, the DD regimen and across both regimens (Figure 2). A 3-year-old boy with influenza B, who received the DD regimen, was given only 3 days of treatment due to nausea and was later admitted to hospital 10 days post last dose of oseltamivir with pneumonia.

Table 1. Paediatric dosing regimens

<table>
<thead>
<tr>
<th>Standard dose oseltamivir</th>
<th>15–23 kg</th>
<th>24–40 kg</th>
<th>&gt;40 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg per day divided into 2 doses</td>
<td>15 mg per day divided into 2 doses</td>
<td>20 mg per day divided into 2 doses</td>
<td>30 mg per day divided into 2 doses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Double dose oseltamivir</th>
<th>15–23 kg</th>
<th>24–40 kg</th>
<th>&gt;40 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg per day divided into 2 doses</td>
<td>25 mg per day divided into 2 doses</td>
<td>30 mg per day divided into 2 doses</td>
<td>40 mg per day divided into 2 doses</td>
</tr>
</tbody>
</table>

Doses are shown and standard dosing adhered to international guidelines for children (≤15 years). Adult standard (>15 years) dose 75 mg twice daily and double dose 150 mg twice daily.
requiring intravenous antibiotics. His viral culture and NAT for influenza were negative at 5 days after first dose of oseltamivir; thus it is unlikely that incomplete viral treatment led to the development of pneumonia.

Virological outcome

Of the 48 cases that were NAT-positive on visit 1, the dosing regimen did not significantly affect virological clearance as determined by NAT-negative swabs by visit 2 (SD 11/23, 47.8% versus DD 17/25, 68%; P=0.16). Of those recruited, 44 were culture-positive on visit one (SD 21/25, 84% versus DD 23/27, 85.2%; P=0.91). There was no difference by dose in virological clearance as determined by culture-negative swabs by visit 2 (SD 20/25, 95.2% versus DD 21/23, 91.3%; P=0.61).

Clearance was not lower in the SD than the DD group for either by influenza A by NAT (SD 3/11, 27.3% versus DD 6/10, 60.0%; P=0.20) or by culture (SD 9/10, 90% versus DD 7/8, 87.5%; P=0.87), nor for influenza B by NAT (SD 8/12, 66.7% versus DD 11/15, 73.3%; P=0.70) or by culture (SD11/11, 100% versus DD 14/15, 93.3%; P=0.76). Influenza subtype was not significantly associated with virological clearance by NAT (influenza A 9/21, 42.9% versus influenza B 19/27, 70.4%; P=0.08) or culture (influenza A 16/18, 88.9% versus influenza B 25/26, 96.2%; P=0.35). There was

Table 3. Virological result by dosing regimen (POCT, NAT or isolation) at recruitment

<table>
<thead>
<tr>
<th>Influenza type and subtype</th>
<th>Standard dose (n=25)</th>
<th>Double dose (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A</td>
<td>9 (36)</td>
<td>8 (29.6)</td>
<td>0.77</td>
</tr>
<tr>
<td>influenza A(H1N1)pdm09</td>
<td>2 (8)</td>
<td>2 (7.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Influenza A H3N2</td>
<td>13 (52)</td>
<td>16 (59.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Influenza B</td>
<td>1 (4)</td>
<td>1 (3.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>No strain documented</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. Of the 50 cases for which an influenza type was determined by point-of-care test (POCT) or nucleic acid test (NAT), 21 (42%) had influenza A and 29 (58%) influenza B. Of the influenza A cases, 4 (19%, all adults) had A/H3N2 subtype.
no significant difference in mean time between swabs 1 and 2 for SD cases (4.65 days; 95% CI 4.17, 5.13) versus DD (4.92 days; 95% CI 4.44, 5.40) nor for those with influenza A (4.86 days; 95% CI 4.36, 5.36) versus influenza B (4.72 days; 95% CI 4.22, 5.22), thus the lack of difference in virological clearance was not confounded by length of time between collection of the two swabs.

Three influenza A(H1N1)pdm09 viruses were OsR, one pre-treatment and two post-treatment (Table 4), all carrying the H275Y mutation. OsR was detected by NAT post-treatment in one case in each of the SD and DD groups (SD 1/23, 4.3% SD versus DD 1/25, 4.0%; \( P=0.95 \)). A mixture of oseltamivir sensitive and resistant viruses was detected in the case receiving the SD regimen, whereas in the case receiving DD only resistant virus was detected. The case that was OsR at enrolment was genotypically related to a cluster of 31 OsR influenza cases, all carrying the H275Y mutation, from the Newcastle region in New South Wales, Australia between May and August 2011 \([10,33,34]\). No cases reported recent contact with Newcastle.
Adverse events
There was a difference in frequency of AEs reported between the two dose regimen groups (SD 4/25, 25% versus DD 13/27, 48%; \( P = 0.02 \)); gastrointestinal (GI) AEs occurred in 16 patients (nausea, vomiting or diarrhoea), with one case of insomnia (DD). The difference remained when solely GI events were analysed (\( P = 0.04 \)). More adults than children reported AEs (\( P = 0.01 \)). Amongst the children from whom AEs were reported, all were \( \leq 6 \) years of age. Two children older than 6 years were recruited (both 14 years old) and neither reported AEs. This age-based difference was significant for influenza A but not influenza B (Table 5), and for both DD and SD (Table 6). This was in the context of no significant relationship between influenza strain and patient age. AEs were not significantly different by recruitment site (general practice 13/35, 37.1% versus The Children’s Hospital 4/17, 23.5%).

Other results
Overall, there were no significant differences in the distribution of influenza strains between either treatment groups, the site of recruitment or age band (data available on request). In total, 49 cases were initially recruited based on positive POCT and 3 by positive rapid NAT; all had a subsequent ‘in-house’ real-time (RT)-PCR performed. Four cases, two in the DD group and two in the SD group, were POCT positive, but both RT-PCR and cell culture negative. Of these, two were influenza B positive by POCT, but the influenza type was not recorded for the other two. Influenza A peaked earlier than influenza B (Figure 4).

Discussion
This study examined the impact of SD versus DD oseltamivir on the selection of OsR virus, safety and effectiveness of therapy. Oseltamivir treatment was associated with a significant increase in overall AEs, particularly GI. The study did not support the hypothesis that DD reduced oseltamivir-resistance, however, it was underpowered. DD oseltamivir was not shown to be more clinically or virologically efficacious. Of those with influenza A, more adults than children reported AE; age-related differences in AE were not shown for influenza B. Thus, influenza type may influence manifestation of GI symptoms. Whilst more adults than children reported AE, there was no statistically significant difference in median age between the two dosing regimens, thus age did not confound the influence of dosing on AEs. The age differential may reflect children’s AEs being recorded by parent/guardian while persons aged \( \geq 15 \) years recorded their own AEs; however, neither of the two 14-year-old children reported AEs, although numbers are too small to draw conclusions. In contrast to our study, a study of 273 pupils and 53 staff at a junior school reported a high frequency of minor AEs to oseltamivir, but did not find a difference in rate of AEs between staff and pupils [35].

The large number of cases of influenza A(H1N1)pdm09 and the lack of A/H3N2 patients recruited amongst the Children’s Hospital recruits reflected national Australian surveillance data for the 2011 influenza season, where most hospitalized cases were predominantly influenza A(H1N1)pdm09 with far fewer influenza A/H3N2 infections [36]. Analysis by age and site of recruitment revealed no statistical difference in distribution of influenza types.

All three cases with OsR influenza A(H1N1)pdm09 experienced an illness with similar severity to other subjects, however the study was underpowered to draw conclusions about the effect of resistance on illness severity. All resistant viruses were similar antigenically to that contained in the 2011 influenza vaccine, highlighting the importance of immunization as a measure to reduce circulating OsR influenza.

### Table 4. Cases with oseltamivir-resistant influenza A(H1N1)pdm09 virus

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender/age</td>
<td>M/5 years</td>
<td>M/5 years</td>
</tr>
<tr>
<td>NAT visit 1</td>
<td>pH1N109</td>
<td>pH1N109</td>
</tr>
<tr>
<td>Viral culture (visit 1)</td>
<td>Influenza A</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Oseltamivir sensitivity (visit 1)</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Dose</td>
<td>D</td>
<td>S</td>
</tr>
<tr>
<td>NAT visit 2</td>
<td>A(H1N1)pdm09</td>
<td>A(H1N1)pdm09</td>
</tr>
<tr>
<td>Viral culture (visit 2)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Oseltamivir sensitivity (visit 2)</td>
<td>Resistant (H275Y)</td>
<td>Mix of sensitive and resistant (H275Y)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Compliance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Three influenza A(H1N1)pdm09 viruses were oseltamivir-resistant, one pre-treatment and two post-treatment, all carrying the H275Y mutation. D, double; M, male; NAT, nucleic acid test; S, standard.
Co-circulation of different influenza strains/types has characterized the recent 2010, 2010/2011, 2011, 2011/2012 influenza seasons in Northern and Southern hemispheres [37–43]. The reported low prevalence of OsR in currently circulating influenza viruses is consistent with our result of 1/51 cases with pre-treatment OsR (2%) [9–11]. However 2/52 (4%) of the cases developed OsR on treatment, both influenza A(H1N1)pdm09. In Stephenson et al.’s study [23] OsR development occurred in 27% (3/11) post-treatment of pre-pandemic influenza A (H1N1) virus amongst children. In contrast, two large studies with 106 cases with influenza A(H1N1)pdm09, one of which recruited predominantly children, did not yield any OsR-influenza A(H1N1)pdm09 strains post-treatment [44,45]. An increasing number of neuraminidase-resistant influenza strains demonstrate mutations associated with reduced susceptibility other than due to H275Y [46–51]. The WHO recommends continued monitoring of OsR prevalence [10,52].

Globally, the WHO has reported that of those from whom OsR influenza was isolated, of the immunocompetent subgroup, 37% had not received prior oseltamivir,
demonstrating community OsR virus circulation [9]. Our case of pre-treatment OsR-influenza A(H1N1)pdm09 was included in the ‘Newcastle cluster’, to date the largest reported community cluster of OsR-influenza A(H1N1)pdm09 infection [10,41]. Whilst this was one of two cases in the cluster found up to 380 km from Newcastle, it appears significant spread of this virus has not developed [32,53]. A review reported several clusters and cases of OsR influenza A(H1N1)pdm09, including untreated cases, and a cluster of six cases of community-acquired OsR influenza A(H1N1)pdm09 was reported from Japan, recently [43,54]. A smaller proportion of OsR influenza A(H1N1)pdm09 cases in the USA received pre-treatment with oseltamivir in the 2010–2011 season (26%) compared to the 2009–2010 (89%) season, suggesting community transmission of the resistant strain [55,56].

A recent randomized controlled trial by Farrar et al. [44] of over 300 hospitalized South East Asian patients with influenza, mostly children, demonstrated that there were no improvements in virological or clinical outcomes with DD over SD oseltamivir. Interestingly, there was also no difference in the AE rate between the two arms of the study (approximately 16% in each arm), a finding which differed from our own; this difference may be partially because our study recruited a lower proportion of children (61% <15 years in our study versus 75% <13.5 years by Farrar et al. [44]), and, in our study, adults experienced more AEs for DD, SD and overall. Farrar et al. [44] did not analyse AE by age. There was no significant difference in mean age between the two dosing regimens in our study, so age did not confound AE incidence between doses. No OsR developed in the 72 patients with influenza A(H1N1)pdm09, half of whom received DD. The study was conducted in hospitalized cases in Asia, conferring potential case severity, ethnic and other differences. Our study is unique in addressing developed world patients with mild (non-hospitalized) influenza and finding significant differences in AEs based on age and dose regimen.

Another recent study from Hong Kong comparing SD versus DD oseltamivir also focused on hospitalized patients, again demonstrating no difference in clinical outcomes or virological clearance, but did not find emergence of OsR. A greater incidence of GI AEs was reported in the DD group when analysed by dose regimen, but no significant difference in AE was reported when intention-to-treat arms were compared [45]. Interestingly, subgroup analysis demonstrated a trend towards increased rate of viral NAT clearance for influenza B with DD oseltamivir, whereas in both our study and Farrar’s et al.’s study [44], there was no difference in clearance of influenza B by day 5. Unlike our study, the Hong Kong study included neither children nor community cases; the average patient was aged in their 60s and no OsR emerged post-treatment.

Two earlier studies demonstrated that higher dose oseltamivir did not reduce influenza viral load more than lower dose oseltamivir [57,58], Treanor et al. [57] revealed no difference in symptom resolution between doses but Hayden et al. [58] did not compare between dose regimens. Neither study compared safety outcomes between doses [57,58]. Another study by Hayden et al. [59] reported a greater frequency of GI AEs in higher dose oseltamivir compared with lower dose but a significance level was not reported. No significant difference in viral clearance was elicited and clinical comparisons were not made [59].

Limitations of our study include the small sample size and the exclusion of both those aged <5 years and immunocompromised patients. Despite our best efforts, we were unable to fulfill our aim of recruiting 125 cases in an attempt to demonstrate a significant difference in rates of development of oseltamivir resistance. In conclusion, this study demonstrated no difference in development of antiviral resistance and no difference in efficacy of different oseltamivir doses, but increased GI adverse effects were elicited with DD oseltamivir.

Acknowledgements

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Disclosure statement

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