Efficacy and Safety of Oseltamivir in Children: Systematic Review and Individual Patient Data Meta-analysis of Randomized Controlled Trials

Ryan E. Malosh, PhD[1]; Emily T. Martin, PhD[1]; Terho Heikkinen, MD[2]; W. Abdullah Brooks MD[3]; Richard J. Whitley, MD[4]; Arnold S. Monto, MD[1]

Author Affiliations

[1] University of Michigan School of Public Health, Ann Arbor MI

[2] University of Turku and Turku Hospital, Turku Finland

[3] Bloomberg School of Public Health, Johns Hopkins University, Baltimore MD

[4] University of Alabama Birmingham, Birmingham AL

Target Journal: Clinical Infectious Diseases

Format Guide:

Word limit: 3000 max	Current: 3000
Abstract: 250 words	Current: 249
Tables/Figures: 7	Current: 7

Key words: influenza, oseltamivir, children, meta-analysis

Summary: We conducted a meta-analysis of the efficacy and safety of oseltamivir in children. Treatment reduced both the duration of illness and risk of otitis media in subjects with influenza. Evaluating efficacy in pediatric patients with asthma may require alternate endpoints.

Abstract

Background: Oseltamivir has been used to treat children with influenza for nearly two decades, with treatment currently approved for infants 2 weeks of age or older, but efficacy and safety remain controversial. Newer randomized placebo controlled trials (RCT), not included in previous meta-analyses, can add to the evidence base.

Methods: We conducted a systematic review to identify RCTs of oseltamivir therapy in children. We obtained individual patient data and examined protocol-defined outcomes. We then conducted a two-stage, random effects meta-analysis to determine the efficacy of treatment in reducing the duration of illness, estimated using differences in restricted mean survival time (RSMT) by treatment group. We also examined complications and safety.

Results: We identified 5 trials including 2561 patients in the intent to treat (ITT) and 1598 in the intent to treat infected (ITTI) population. Overall, oseltamivir treatment significantly reduced the duration of illness in the ITTI population (RMST difference -17.6 hours 95% CI: -34.7 to -0.62 hours). In trials that enrolled patients without asthma, the difference was larger (-29.9 hours 95% CI -53.9 to -5.8 hours). Risk of otitis media was 34% lower in the ITTI population. Vomiting was the only adverse event with a significantly higher risk in the treatment group.

Conclusion: Despite substantial heterogeneity in pediatric trials, we found that treatment with oseltamivir significantly reduced the duration of illness in those with influenza and lowered the risk of developing otitis media. Alternative endpoints may be required to evaluate the efficacy of oseltamivir in pediatric patients with asthma.

Introduction

Globally, influenza is an important contributing cause of hospitalization and mortality in children less than 5 years old [1]. Vaccines, though only moderately effective, remain the most effective way to prevent illnesses [2–4]. Thus, prevention strategies must be coupled with treatment of influenza virus infections to minimize the burden of disease.

Two neuraminidase inhibitors, inhaled zanamivir and oral oseltamivir, were licensed by the Food and Drug Administration (FDA) in 1999 for treatment of uncomplicated influenza. The results of the pivotal licensure studies [5–7] were remarkably similar, even though the two drugs were dissimilar in their mode of administration and metabolism. In the nearly two decades since, zanamivir has had only limited use, leaving oseltamivir as the principal option for the treatment of uncomplicated seasonal influenza and for stockpiling and use during pandemics [8]. Following the experience with severe disease in young children during the 2009 pandemic, oseltamivir is now licensed for children down to two weeks of age [9].

Large observational studies have documented evidence of effectiveness and safety of oseltamivir use [10–12]. Significant reductions of severe outcomes were found among hospitalized adults, but these effects were attenuated and not significant among children [13]. Oseltamivir remains controversial in some quarters for several reasons, including safety concerns. [14–16], This controversy has focused on randomized controlled trials (RCTs) that were the basis for licensure, mainly due to the potential for bias in analysis and the availability of data from unpublished studies [8,17,18]. A recent meta-analysis, using individual-level data from all RCTs of timely (≤ 48 hours from symptom onset) oseltamivir treatment in outpatients with uncomplicated influenza, confirmed significant reductions in duration of illness and complications in those randomized and infected, but not among the uninfected [19]. To avoid complexities due to heterogeneity in pediatric trials, the analysis was limited to adults. Here we extend the previous work to RCTs in children < 18 years old. Following a systematic review

which identified two recently published trials, we estimated the efficacy of timely oseltamivir treatment for uncomplicated influenza comparing children treated in the outpatient setting to those receiving placebo.

Methods

Systematic review

We searched PubMed, MEDLINE, EMBASE, and the Cochrane Library for clinical trials published between January 1, 1997 and May 1, 2016 using medical subject heading (MeSH) terms to identify oseltamivir studies in children with influenza virus infection. Unique titles and abstracts were reviewed for eligibility using pre-specified PICOS criteria (Figure 1). Non-primary literature including reviews, meta-analyses or secondary analyses were excluded. We reviewed references lists of systematic reviews and previous meta-analyses and contacted investigators to identify additional trials. Data was obtained from Roche via the Multiparty Group for Advice on Science (MUGAS) for two published (WV15758, WV15759/WV15871) and one unpublished trial (NV16871); data from two additional trials (NCT00707941 and NCT00593502) were obtained directly from investigators (Supplemental Table 1). The risk of bias was evaluated using the Cochrane tool to describe the data quality from each trial (Supplemental Table 2). The protocol for this systematic review was registered with PROSPERO (July 14, 2016, 42016038982) prior to initiation of the review.

Meta-analysis

We conducted a two-stage, individual participant data meta-analysis of the efficacy of timely oseltamivir treatment in reducing the duration of influenza-associated acute respiratory illness [20]. Kaplan-Meier plots of duration of illness were initially assessed by treatment group for individual trials and for all trials pooled (Supplemental figures 1 and 2). Treatment effect estimates (time ratio) by trial were obtained from an accelerated failure time (AFT) model with a

generalized F distribution due to violation of the proportional hazard assumption in some trials [21]. The difference in restricted mean survival time (RMST) for duration of illness by treatment group and 95% confidence intervals were also estimated for each trial individually [22]. We then conducted a random effects meta-analysis with maximum likelihood approach to estimate heterogeneity between trials. All analyses were performed using R version 3.3.2.

Efficacy analyses were first restricted to subjects who received at least one dose of study drug and who had laboratory confirmed influenza virus infection (ITTI: intention-to-treat infected population), and repeated for the intention-to-treat (ITT) population which included both children with and without influenza virus infection, all of whom were randomized to receive treatment or placebo. We also conducted a meta-regression to evaluate trial characteristics (inclusion of only patients with asthma, inclusion of adolescents, treatment within 24 hours, and outcome definition) that were hypothesized to confound the overall treatment effect. We then conducted meta-analyses for additional outcomes including complications due to influenza and adverse events.

Main outcome

The primary endpoint for this meta-analysis, duration of illness in hours, was comprised of the following study specific endpoints: three trials (WV15759/WV15871, WV15758, and NCT0059302) used the terminology resolution of illness to describe the time from the start of treatment to when the following conditions were met for at least 24 hours: child was afebrile, cough or rhinitis were either absent or mild, and child had returned to normal activities. In the remaining trials duration of illness was defined as the time from the start of treatment to resolution of influenza symptoms (NV16871), or resolution of major signs and symptoms (e.g. fever, tachypnea, difficult/noisy breathing, cough and any danger sign) (NCT00707941).

Complications and Adverse Events

Binary outcomes (e.g. complications, adverse events) were also analyzed using a two-stage meta-analysis, risk ratios and standard errors for these outcomes were estimated for individual trials using log-binomial regression models [23]. Trials with zero events in both arms were excluded from those specific analyses.

We evaluated the efficacy of oseltamivir treatment in reducing the risk of the following complications: lower respiratory tract complication (LRTC), otitis media, and hospitalization >48 hours after first study drug intake. Subjects taking antibiotics at randomization were excluded from these secondary analyses. Complications were determined by clinician diagnosis, as defined in individual study protocols.

Safety outcomes included serious adverse events and nausea, vomiting, and diarrhea. Adverse events were analyzed for 'on treatment' periods only. An adverse event was 'on treatment' if it occurred between first study drug intake and up to 48 hours after last dose of study drug.

Pooled analysis

We also estimated the efficacy of oseltamivir treatment in pooled analyses stratified by subgroups of interest. We estimated the time ratio and RMST difference among those receiving treatment early (i.e. within 24 hours of onset), by age group (< 6 years, 6-11 years, 12-17 years), among individuals with and without asthma, and among those with and without laboratory confirmed influenza virus infection, adjusted for trial.

Results

Search results

Our search terms (Supplementary material) identified 97 citations. After excluding duplicates, we obtained the full text of 68 unique studies. Twenty-four studies were excluded because they were not primary literature, and 40 were excluded for not meeting all of the

PICOS criteria (Figure 1). Four published studies met all inclusion criteria. We identified one additional unpublished trial; thus 5 trials were included in the final analysis.

Description of trials and participant characteristics

Three (WV15758 [24], WV15759/WV15871 [25], NV16871 [26]) were performed between 1998 and 2004 (Table 1). Children were eligible if they were enrolled within 48 hours of symptom onset, had fever ≥37.8°C and at least one respiratory symptom (cough or coryza). Trial NCT00707941, conducted by the International Center for Diarrhoeal Diseases, Bangladesh (icddr,b) from May 2008 through December 2010, included participants only if they presented at the study clinic with a rapid test positive for influenza [27]. A trial of early treatment (NCT00593502) was conducted during the 2007-2008 and 2008-2009 seasons, included only participants < 4 years old presenting at the study clinic within 24 hours of symptom onset [28]. Of note, there was variation between trials in the definition and terminology used to describe the duration of illness (Table 1). This outcome was alternatively referred to as alleviation of symptoms or resolution of illness.

We examined participant characteristics by treatment group overall and by trial (Table 2). In total, the intent to treat (ITT) population consisted of 2561 participants randomized within 48 hours of symptom onset to receive either oseltamivir (n=1281) or placebo (n=1280). NCT00707941 enrolled 1190 participants in total, 796 of whom were included in this meta-analysis because they were randomized within 48 hours of symptom onset. Three-hundred and ninety four were randomized >48 hours after onset and, therefore, did not meet our inclusion criteria. Two trials (NV16871 and WV15789/15871) were restricted to children with asthma. The pooled ITTI population consisted of 1598 (62%) individuals 770 (48%) of whom received timely oseltamivir treatment. We found no significant differences in the proportion treated by any of the characteristics examined (Table 2). Overall, forty-six (1.8%) children were missing data on

duration of illness; 26 from WV15758, 3 from WV15759/15871 and 17 from NCT00593502, missing data did not differ by treatment status.

Meta-analysis

Overall, there was a significant reduction in the duration of illness among those receiving timely oseltamivir treatment (RMST difference: -17.6 hours 95% CI: -34.5 to -0.7 hours) (Figure 2). An indicator for enrolling only asthma patients was significant in the meta-regression for the ITTI population (p=0.03), indicating heterogeneity between asthma-only and combined populations. Thus, we stratified the meta-analysis based on trial inclusion criteria in regards to asthma status. The effect of treatment was larger in trials that enrolled children regardless of asthma status (RMST -29.9 hours 95% CI: -53.9 to -5.8 hours). For trials enrolling only patients with asthma, there was no effect of treatment (Figure 2). Reductions in the duration of illness were attenuated in the ITT population (Supplemental Figure 2), but remained significant (RMST difference 8.4 hours, 95%CI: -16.7 to -0.01 hours) (Supplemental Figure 3).

Complications

In the ITTI population (n=1598) there were fewer cases of LRTC >48 hours after first study drug intake in the oseltamivir group compared to the placebo group (29/770 [4%] vs 38/828 [5%], RR: 0.75, 95% CI: 0.37, 1.52), but the difference was not statistically significant (Figure 3). There was evidence of a 34% reduction in risk of developing otitis media in the ITTI population (RR: 0.66, 95% CI: 0.47-0.95). In the ITT population (n=2458), the effect of treatment on developing otitis media was attenuated and no longer significant (RR: 0.98, 95%CI 0.77, 1.26). There were too few hospitalizations to reach meaningful conclusions (ITTI 4/770 [0.5%] oseltamivir compared to 3/825 [0.3%] placebo).

Safety

We found an increased relative risk (RR) of vomiting in the treatment group (RR: 1.63, 95% CI: 1.30, 2.04) but no evidence of an increased risk of nausea, diarrhea, or severe adverse events (SAE) among 2558 subjects in the safety population (Table 3). SAE were very rare in both the oseltamivir (11/1074 [1%]) and placebo (4/1078 [0.4%]) groups. In the trials that recorded data there was also no difference in withdrawal from treatment (26/676 [4%] oseltamivir vs 27/682 [4%] placebo, p=0·93) or withdrawal due to an adverse event (8/676 [1%] versus 8/682 [1%], p=0·99) by treatment group.

Pooled analysis

Finally we conducted a pooled analysis, combining data across trials, to examine subgroups of interest. In stratified analyses adjusting for trial we observed a larger difference in RMST for individuals who received early treatment (< 24 hours) compared to those who received treatment 24-48 hours after onset (-22.8 hours 95% CI: -29.4 to -16.2 hours vs -4.4 95% CI:-15.5 to 6.5 hours). We observed the largest reduction in duration of illness among adolescents (12-17 years old), though confidence intervals of age stratified estimates overlapped (Figure 4). We found no effect of treatment in children with asthma but a large difference in those without asthma (-34.9 hours, 95%CI: -46.4 to -23.4 hours). We also found no effect of treatment compared to placebo among uninfected participants (3.1 hours 95%CI:-5.9 to 12.1 hours), while among infected individuals there was a significant reduction in duration of illness consistent with the pooled effect from the meta-analysis (-17.5 hours 95%CI:-23.2 to -11.8 hours). Results of pooled analyses, adjusting for potential confounders, for complications (Supplemental table 3) and safety (Supplemental table 4) outcomes were similar to those from the meta-analyses described above.

Discussion

In the current analysis, we demonstrated a reduction in the duration of illness of approximately 18 hours among children receiving timely oseltamivir treatment compared to

placebo. We additionally found that treatment reduced the risk of otitis media and that there was little evidence of safety issues, apart from vomiting. A recent meta-analysis of all adult RCTs found a reduction in duration of illness in the ITTI population of 25 hours [19]. The identified adult trials, including published and unpublished work, were all conducted about the time of licensure. The study populations varied in some trials (e.g. older adults or those with underlying conditions), but all trials used a similar endpoint, termed alleviation of illness. This endpoint was defined as absence of fever, but other symptoms could be either mild or absent. In contrast, there was much more variation in both study population and endpoints in the pediatric studies included in this analysis. The largest pediatric trial, for example, was conducted 10 years after licensure, in urban Bangladesh. This setting was chosen to estimate the efficacy of oseltamivir in conditions with high levels of crowding and poor sanitation. The primary outcome, duration of clinical illness, was defined by no sign of illness, including fever, danger signs, or other indications requiring clinical referral [27]. Two other trials included only children with asthma, one limited to children > 6 years, and each used a different primary endpoint. To address this heterogeneity we performed a random effects meta-analysis and used the outcome which was as close as possible to the definition of alleviation from the adult trials. We also examined the sensitivity of our overall estimate to each trial by systematically excluding trials and repeating the analysis (Supplemental Table 5). When the Bangladesh trial was removed the estimated reduction in duration increased to 20 hours. It is perhaps not surprising, given the potential for effect modification by crowding and other factors, that the estimated reduction including the Bangladesh trial was lower.

We also found that the overall estimate was attenuated in the per-protocol (ITT) population, a result of no significant difference in duration of illness among those not infected with influenza viruses. This confirms a similar finding from the meta-analysis of adult trials and suggests that the reduction in illness duration is attributable to a specific antiviral effect and not

generalized anti-inflammatory activity, as has been posited [14]. That the reduction detected was a result of antiviral effect is confirmed by the greater reduction in duration when oseltamivir was given within 24 hours of onset [29]. It is also clear that the definition of infection did not affect the results (Supplemental figure 4).

The major outliers in this analysis were the trials including only children with asthma. The pooled estimate for the three trials that did not specifically enroll asthma patients was a reduction in illness duration of 29.9 hours; closer to that found in the adult meta-analysis [19]. There is no clear reason to hypothesize a different antiviral effect in asthmatic children compared to healthy children. Rather the difference in efficacy may be explained by the difficulty in recognition of clinical illness endpoints in those with underlying respiratory conditions. Alternate endpoints, such as improvements in pulmonary function or the duration of viral shedding, may be more relevant in future studies of asthmatic children. Molecular methods to determine respiratory viral load have become standard since the original trials and may help separate the role of viral replication and symptoms in these children [30,31].

We found no evidence of an increase in the risk of nausea or severe adverse events, but did detect an increase in the risk of vomiting in those receiving oseltamivir. These results are consistent with previous analyses [16,19,32]. While the ITT population was relatively large, it might not be large enough to detect more infrequent adverse events. For that purpose, it is useful to look at the evaluations conducted in the course of the pediatric studies resulting in the approval in the US in children down to age 2 weeks [9,33]. In these studies vomiting was also the only adverse effect seen more often with oseltamivir compared with placebo [9]. That approval was an explicit recognition of the need for an antiviral to treat influenza virus infections in this vulnerable population.

Reduction of complications is a major rationale for antiviral treatment of influenza virus infection in adults and the basis for policy recommendations. Not surprisingly, lower respiratory

complications were infrequent in the current analysis which mainly included children without serious underlying conditions. Overall, there were fewer complications in the treated group but the difference was not statistically significant. Importantly, we did find a significant reduction of 34% in the risk of developing otitis media in those receiving oseltamivir treatment. Similar reductions have been found in individual studies [24,28] and the pivotal evaluations of live attenuated influenza vaccine in children under 6 years old [34,35]. These observations further confirm the role of influenza as an etiologic agent of otitis media and the role of both prophylaxis and treatment in its prevention.

During the 2009 pandemic the need for antiviral treatment of young children with influenza was reinforced as they were particularly vulnerable to severe illness [36–38]. A meta-analysis of individual patient data from observational studies conducted during that period showed a highly significant effect of oseltamivir in preventing mortality among hospitalized adults but not among children [13]. Our analysis is reassuring that in uncomplicated influenza oseltamivir appears to be as safe and effective in children as among adults. With the appropriate dose now established, there does not appear to be any scientific reason why it should be of lower efficacy, even in cases of severe disease. Of particular importance is the evidence for the prevention of otitis media as this is a relatively frequent complication of influenza virus infection with the potential for long term consequences on language development and learning. Our findings support current policy [39] and the position of the American Academy of Pediatrics [40], and reinforce the recommendation that treatment is most useful when started early after illness onset.

Notes

Acknowledgement

We thank Alicia Fry for her support in acquisition and interpretation of data and her overall guidance throughout the project.

Funding and Disclosure

This study was funded by the Multiparty Group for Advice on Science (MUGAS) Foundation through an unrestricted grant from Roche Pharmaceuticals. Neither party had a role in analysis, interpretation, reporting or the decision to submit for publication. We thank Roche for providing the data and answering data specific queries.

Potential conflicts of interest

REM, ETM, TH and WAB report no conflicts of interest. RJW reports fees as a board member of Gilead Sciences. ASM reports consulting fees from Roche related to the submitted work and from Seqirus outside the submitted work.

References

1. Lafond KE, Nair H, Rasooly MH, et al. Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982–2012: A Systematic Analysis. PLOS Med. **2016**; 13(3):e1001977.

2. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis. **2016**; 16(8):942–951.

3. McLean HQ, Thompson MG, Sundaram ME, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clin Infect Dis. **2014**; 59(10):1375–85.

4. Ohmit SE, Petrie JG, Malosh RE, Fry AM, Thompson MG, Monto AS. Influenza vaccine effectiveness in households with children during the 2012-2013 season: assessments of prior vaccination and serologic susceptibility. J Infect Dis. **2015**; 211(10):1519–28.

5. Hayden FG, Osterhaus ADME, Treanor JJ, et al. Efficacy and Safety of the Neuraminidase Inhibitor Zanamivir in the Treatment of Influenzavirus Infections. N Engl J Med. **1997**; 337(13):874–880.

6. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA. **2000**; 283(8):1016–1024.

7. Nicholson K, Aoki F, Osterhaus A, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. The Lancet. **2000**; 355(9218):1845–1850.

8. Hurt AC, Kelly H. Debate Regarding Oseltamivir Use for Seasonal and Pandemic Influenza. Emerg Infect Dis. **2016**; 22(6):949–955.

9. Kimberlin DW, Acosta EP, Prichard MN, et al. Oseltamivir Pharmacokinetics, Dosing, and Resistance Among Children Aged <2 Years With Influenza. J Infect Dis. **2013**; 207(5):709–720.

10. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med. **2012**; 156(7):512–524.

11. Bueno M, Calvo C, Méndez-Echevarría A, et al. Oseltamivir treatment for influenza in hospitalized children without underlying diseases. Pediatr Infect Dis J. **2013**; 32(10):1066–1069.

12. Blumentals WA, Song X. The Safety of Oseltamivir in Patients with Influenza: Analysis of Healthcare Claims Data from Six Influenza Seasons. Medscape Gen Med. **2007**; 9(4):23.

13. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. **2014**; 2(5):395–404.

14. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. **2014**; 348:g2545.

15. Michiels B, Van Puyenbroeck K, Verhoeven V, Vermeire E, Coenen S. The value of neuraminidase inhibitors for the prevention and treatment of seasonal influenza: a systematic review of systematic reviews. PloS One. **2013**; 8(4):e60348.

16. Shun-Shin M, Thompson M, Heneghan C, Perera R, Harnden A, Mant D. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. BMJ. **2009**; 339:b3172.

17. Doshi P, Jefferson T, Mar CD. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLOS Med. **2012**; 9(4):e1001201.

18. Nguyen-Van-Tam JS, Venkatesan S, Muthuri SG, Myles PR. Neuraminidase inhibitors: who, when, where? Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. **2015**; 21(3):222–225.

19. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. The Lancet. **2015**; 385(9979):1729–1737.

20. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med. **2017**; 36(5):855–875.

21. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. John Wiley & Sons; 2011.

22. Royston P, Parmar MKB. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Stat Med. **2011**; 30(19):2409–2421.

23. McNutt L-A, Wu C, Xue X, Hafner JP. Estimating the Relative Risk in Cohort Studies and Clinical Trials of Common Outcomes. Am J Epidemiol. **2003**; 157(10):940–943.

24. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J. **2001**; 20(2):127–133.

25. Johnston SL, Ferrero F, Garcia ML, Dutkowski R. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. Pediatr Infect Dis J. **2005**; 24(3):225–232.

26. Roche. A Double-Blind, Randomized, Stratified, Placebo-Controlled Study of Oseltamivir in the Treatment of Influenza in Children with Asthma (Protocol NV16871).

27. Fry AM, Goswami D, Nahar K, et al. Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: A randomised placebo-controlled trial. Lancet Infect Dis. **2014**; 14(2):109–118.

28. Heinonen S, Silvennoinen H, Lehtinen P, et al. Early oseltamivir treatment of influenza in children 1-3 years of age: A randomized controlled trial. Clin Infect Dis. **2010**; 51(8):887–894.

29. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. J Antimicrob Chemother. **2003**; 51(1):123–129.

30. Ng S, Cowling BJ, Fang VJ, et al. Effects of Oseltamivir Treatment on Duration of Clinical Illness and Viral Shedding and Household Transmission of Influenza Virus. Clin Infect Dis. **2010**; 50(5):707–714.

31. Li C-C, Wang L, Eng H-L, et al. Correlation of Pandemic (H1N1) 2009 Viral Load with Disease Severity and Prolonged Viral Shedding in Children. Emerg Infect Dis. **2010**; 16(8):1265–1272.

32. Kimberlin DW, Shalabi M, Abzug MJ, et al. Safety of Oseltamivir Compared With the Adamantanes in Children Less Than 12 Months of Age. Pediatr Infect Dis J. **2010**; 29(3):195–198.

33. Rath BA, Brzostek J, Guillén S, et al. Safety, virology and pharmacokinetics of oseltamivir in infants with laboratory-confirmed influenza: a Phase I/II, prospective, open-label, multicentre clinical trial. Antivir Ther. **2015**; 20(8):815–825.

34. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med. **1998**; 338(20):1405–1412.

35. Block SL, Heikkinen T, Toback SL, Zheng W, Ambrose CS. The efficacy of live attenuated influenza vaccine against influenza-associated acute otitis media in children. Pediatr Infect Dis J. **2011**; 30(3):203–207.

36. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April–June 2009. N Engl J Med. **2009**; 361(20):1935–1944.

37. Libster R, Bugna J, Coviello S, et al. Pediatric Hospitalizations Associated with 2009 Pandemic Influenza A (H1N1) in Argentina. N Engl J Med. **2010**; 362(1):45–55.

38. Louie JK, Acosta M, Winter K, et al. Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California. JAMA. **2009**; 302(17):1896–1902.

39. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. **2011**; 60(1):1–24.

40. Committee on Infectious Diseases AA of P. Red Book®: 2015 Report of the Committee on Infectious Diseases [Internet]. 30th ed. Printed in the United States of America: American Academy of Pediatrics; 2015. Available from: http://online.statref.com/Document.aspx?docAddress=ecMaf2LomNP2lW1_uz9UkQ%3d%3d

Table 1. Description of randomized controlled trials of efficacy of oseltamivir in pediatric populations

Trial	**WV15758** [24]	**WV15759/WV15871** [25]	**NV16871** [26]	**NCT00707941** [27]	**NCT00593502** [28]
Description	*Otherwise healthy children (1-12y) - <48h of symptom onset*	*Children with asthma (≥6y - ≤12y) - <48h of symptom onset*	*Children with asthma (≥6y - ≤17y) - <48h of symptom onset*	*Age +1yr, no upper age limit (89% <18yrs, ~80% <=10yrs) - within 5 days symptom onset*	*Children (1-3y) - early treatment (<=24h of symptom onset)*
Location	USA, Canada	Europe, Israel, USA, Canada, Argentina, Australia, Chile, China, New Zealand, S. Africa	Europe, Israel	Bangladesh	Finland
Numbers of ITT patients	695 (planned = 680)	334 (planned = 500)	329 (planned = 392)	796 (<48hr from onset)[1]	408 (planned = 308)
Number (%) ITTI patients	452 (65%) (planned = 340) - 217 oseltamivir - 235 placebo	179 (54%) (planned = 250) - 84 oseltamivir - 95 placebo	94 (29%) (planned = 196) - 43 oseltamivir 51 placebo	796 (<48hr from onset)[1] - 398 oseltamivir - 396 placebo	98 (24%) (planned = 154) - 37 oseltamivir - 61 placebo
Randomization	1:1 Stratified by presence/absence of acute otitis media (baseline clinical diagnosis)	1:1 Stratified by class of asthma (mild or moderate/severe).	1:1 Stratified by class of asthma (mild or moderate/severe) and time from onset of influenza symptoms to treatment start.	1:1 Stratified by <48h and 48+h since symptom onset. Permuted blocks with variable length between 2 and 8.	1:1 Randomized in blocks of 4. Randomization, labeling and packaging of study drugs performed by Roche.
Laboratory assays for detection of influenza	Virus culture, serology	Virus culture, serology	Virus culture, serology	RT-PCR, virus isolation	Virus culture, time-resolved fluoroimmunoassay, RT-PCR
Duration of illness definition	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity	Time to illness onset to resolution of influenza symptoms	Time from illness onset to resolution of major symptoms (fever, tachypnea, difficult/noisy breathing, cough, and any danger sign)	Time from illness onset to presence of mild or absent cough and rhinitis, afebrile, return to normal activities,

[1] 1190 enrolled and randomized total, 796 <48 hours from onset. Separate randomization for those enrolled >48 hours from onset

Table 2. Characteristics of trial participants by treatment and trial

Trial	WV15758		WV15759/WV15871		NV16871	
	Placebo	Oseltamivir	Placebo	Oseltamivir	Placebo	Oseltamivir
ITT population	351	344	164	165	164	170
ITTI population (%)	225 (64.1)	209 (60.8)	51 (31.1)	43 (26.1)	95 (57.9)	84 (49.4)
Age Category (%)						
≤ 5 years	197 (56.1)	193 (56.1)	0 (0.0)	0 (0.0)	2 (1.2)	4 (2.4)
6-11 years	138 (39.3)	139 (40.4)	90 (54.9)	93 (56.4)	151 (92.1)	145 (85.3)
12-17 years	16 (4.6)	12 (3.5)	74 (45.1)	72 (43.6)	11 (6.7)	21 (12.4)
≥18 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Male (%)	179 (51.0)	171 (49.7)	108 (65.9)	107 (64.8)	101 (61.6)	111 (65.3)
Influenza Vaccine Current Season (%)	10 (2.8)	11 (3.2)	--	--	34 (20.7)	31 (18.2)
Influenza Vaccine Prior Season (%)	13 (3.7)	21 (6.1)	--	--	37 (22.6)	39 (22.9)
Asthma (%)	0 (0.0)	0 (0.0)	164 (100.0)	165 (100.0)	164 (100.0)	170 (100.0)

Trial	NCT00707941		NCT00593502		Overall		
	Placebo	Oseltamivir	Placebo	Oseltamivir	Placebo	Oseltamivir	p value
ITT population	396	398	205	204	1280	1281	
ITTI population	396 (100)	398 (100)	61 (29.8%)	37 (18.1%)	828 (65.5)	770 (60.8)	
Age Category (%)							
≤ 5 years	222 (56.1)	213 (53.5)	205 (100.0)	204 (100.0)	626 (48.9)	614 (47.9)	0.927
6-11 years	98 (24.7)	102 (25.6)	0 (0.0)	0 (0.0)	477 (37.3)	479 (37.4)	
12-17 years	28 (7.1)	31 (7.8)	0 (0.0)	0 (0.0)	129 (10.1)	136 (10.6)	
≥18 years	48 (12.1)	52 (13.1)	0 (0.0)	0 (0.0)	48 (3.8)	52 (4.1)	
Male (%)	208 (52.5)	218 (54.8)	123 (60.0)	106 (52.0)	719 (56.2)	713 (55.7)	

Influenza Vaccine Current Season (%)	--	--	51 (24.9)	52 (25.5)	95 (8.5)	94 (8.4)	0.825
Influenza Vaccine Prior Season (%)	0 (0.0)	0 (0.0)	--	--	50 (4.5)	60 (5.4)	1.00
Asthma (%)	--	--	6 (2.9)	7 (3.4)	334 (37.8)	342 (38.7)	0.379

Table 3. Meta-analysis of adverse event outcomes. Relative risk estimated from log-binomial regression models.

	Placebo N	**Oseltamivir N**	**RR (95% CI)**			
Study			Vomiting	Nausea	Diarrhea	Severe Adverse Events
WV15758	351	344	1.67 (1.08-2.56)	0.96 (0.45-2.02)	0.83 (0.52, 1.31)	1.53 (0.26-11.70)
WV15759/WV15871	164	170	1.45 (0.83-2.53)	0.48 (0.13-1.50)	0.80 (0.36-1.81)	2.41 (0.53-16.68)
NV16871	164	165	3.23 (1.08-9.70)	1.21 (0.37-4.12)	--	--
NCT00707941	396	398	1.71 (0.90-3.25)	6.96 (0.86-56.35)	0.80 (0.53-1.21)	--
NCT0593502	202	207	1.54 (1.07-2.20)	--	0.96 (0.74-1.25)	--
Overall	1281	1277	1.63 (1.30-2.04)	1.10 (0.45-2.71)	0.89 (0.74-1.08)	1.98 (0.59-6.52)

1 Figure 1. Results of the systematic review

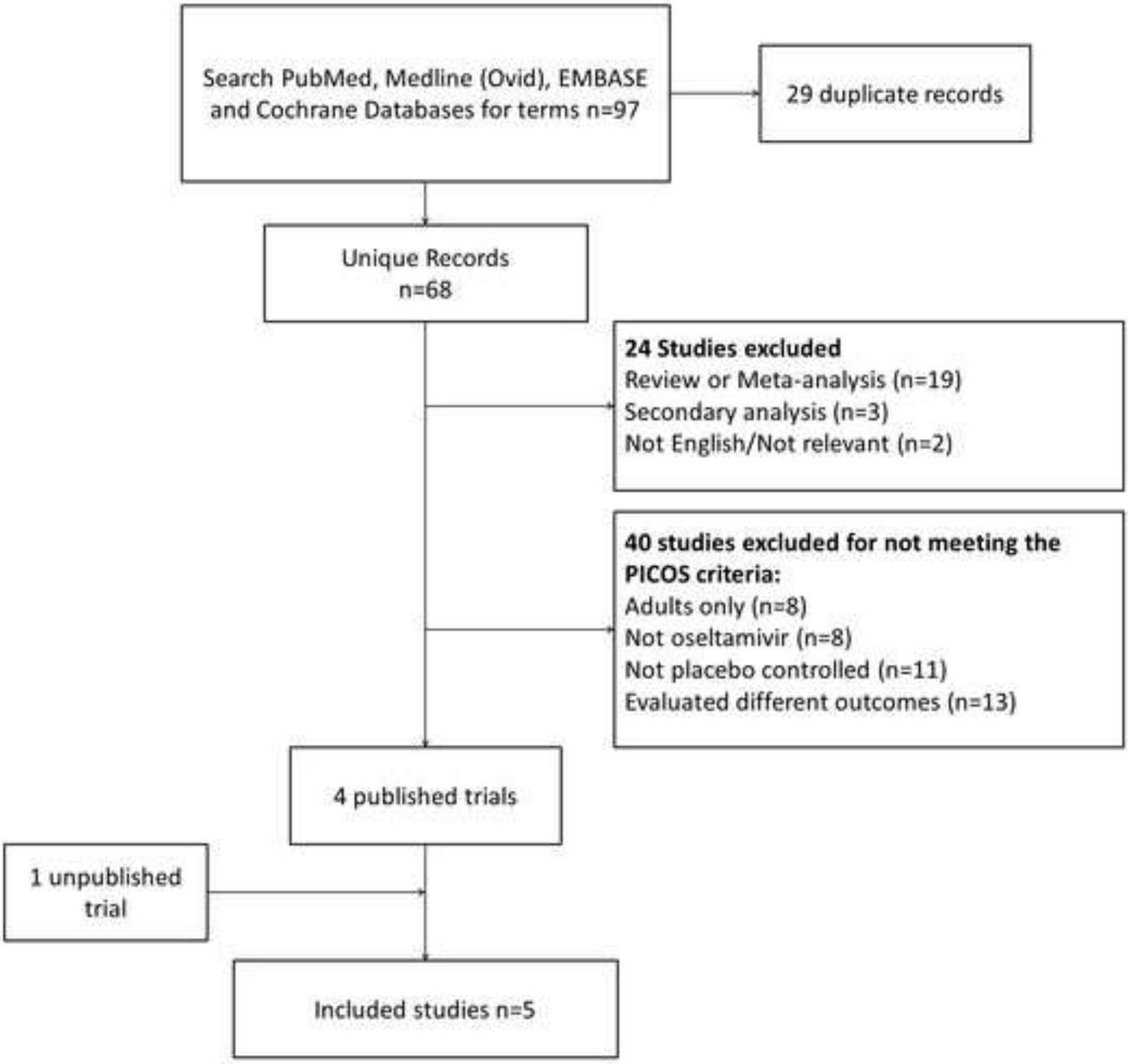
Figure 2. Forest plot, random effects meta-analysis of the efficacy of oseltamivir treatment in reducing duration of illness as measured by the difference in restricted mean survival time (RMST) and time ratio from accelerated failure time (AFT) models in the ITTI population

Figure 3. Forest plot, random effects meta-analysis of the relative risk of developing complications in the ITTI population a) Lower respiratory tract complications (LRTC) b) otitis media. Relative risk estimated from log-binomial regression models.

Figure 4. Forest plot, pooled analysis estimating the time ratio from AFT models with generalized F distribution and restricted mean survival time (RMST) difference and 95% confidence interval (CI) for subject receiving oseltamivir compared to placebo stratified by subgroups of interest and controlling for trial.

Figure 1 (.tif and .eps files only)

Click here to download Figure (.tif and .eps files only) Figure 1 Search Results 082417.tif



Duration of Illness − ITTI population

Trial	Oseltamivir N	Placebo N	Time Ratio (95% CI)	RMST Difference [95% CI]
Asthma Trials				
NV16871	43	51	1.02 [0.70;1.49]	0.9 [−31.4; 33.3]
WV15759/WV15871	83	95	0.95 [0.77;1.16]	3.7 [−20.1; 27.5]
Random effects model	**126**	**146**		**2.2 [−12.5; 16.9]**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.85				
Non Asthma Trials				
WV15758	209	225	0.73 [0.64;0.84]	−31.8 [−47.4; −16.2]
NCT00707941	398	396	0.87 [0.77;0.98]	−10.5 [−20.8; −0.1]
NCT00593502	37	61	0.67 [0.47;0.96]	−46.9 [−81.9; −11.8]
Random effects model	**644**	**682**		**−29.9 [−53.9; −5.8]**
Heterogeneity: I^2 = 88%, τ^2 = 379.6, p < 0.01				
Random effects model	**770**	**828**		**−17.6 [−34.5; −0.7]**
Heterogeneity: I^2 = 83%, τ^2 = 287.4, p < 0.01				

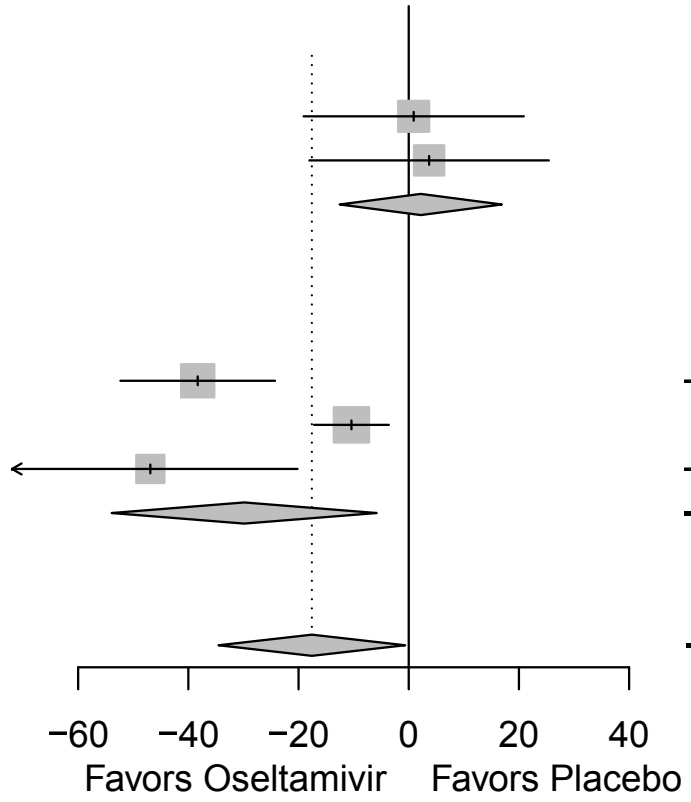


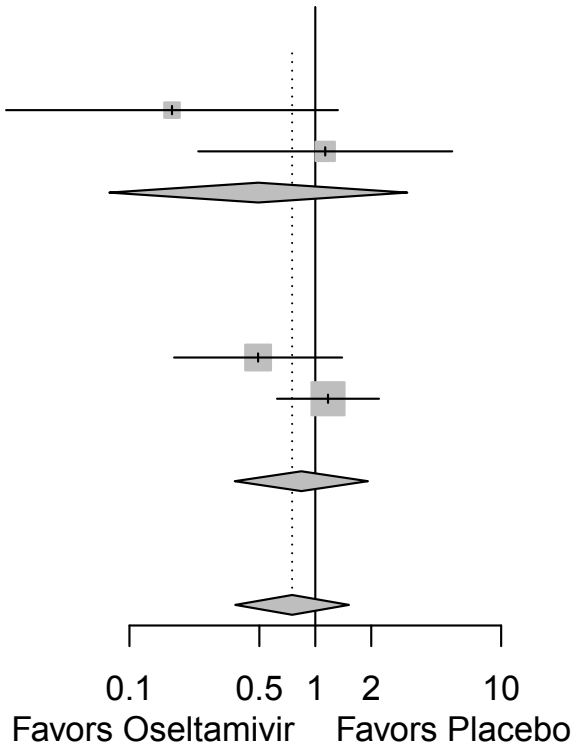
Figure 3 (.tif and .eps files only)

Click here to download Figure (.tif and .eps files only) Figure 3 Complications 100217.eps

A

Lower Respiratory Tract Complications - ITTI Population

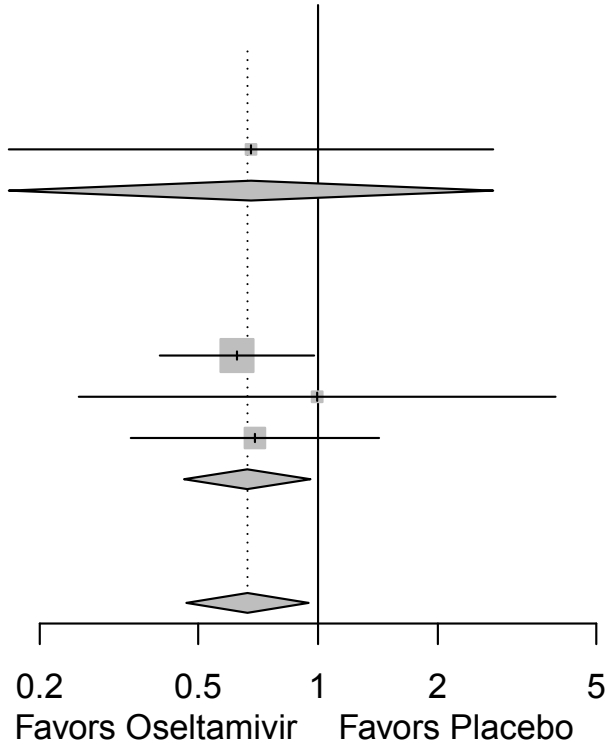
Trial	Oseltamivir N	Placebo N	RR	95% CI
Asthma Trials				
NV16871	43	51	0.17	[0.02; 1.32]
WV15759/WV15871	83	95	1.13	[0.23; 5.45]
Random effects model			**0.49**	**[0.08; 3.12]**
Heterogeneity: I^2 = 52%, τ^2 = 0.9297, p = 0.15				
Non−Asthma Trials				
WV15758	209	225	0.49	[0.17; 1.39]
NCT00707941	398	396	1.17	[0.62; 2.20]
NCT0059302[a]	37	61		
Random effects model			**0.84**	**[0.37; 1.92]**
Heterogeneity: I^2 = 49%, τ^2 = 0.1823, p = 0.16				
Random effects model	**770**	**828**	**0.75**	**[0.37; 1.52]**
Heterogeneity: I^2 = 34%, τ^2 = 0.1765, p = 0.21				



B

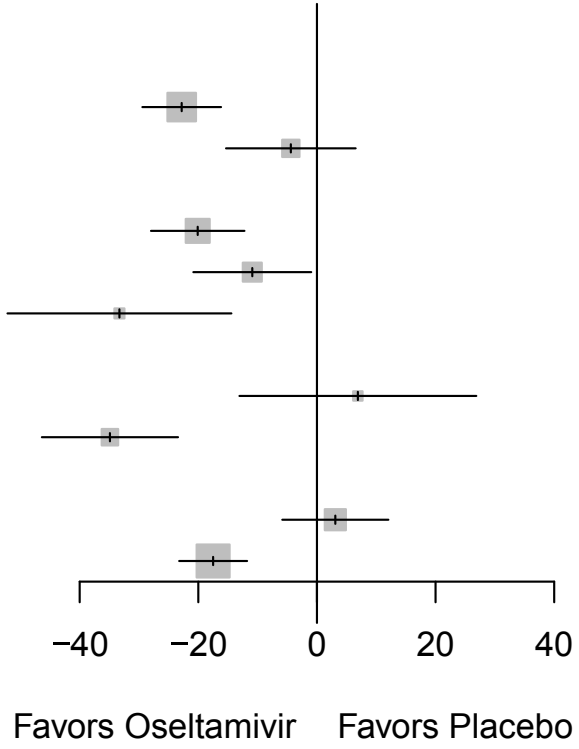
Otitis Media - ITTI Population

Trial	Oseltamivir N	Placebo N	RR	95% CI
Asthma Trials				
NV16871[b]	43	51		
WV15759/WV15871	83	95	0.68	[0.17; 2.75]
Random effects model			**0.68**	**[0.17; 2.75]**
Heterogeneity: Not applicable				
Non−Asthma Trials				
WV15758	209	225	0.63	[0.40; 0.98]
NCT00707941	398	396	0.99	[0.25; 3.95]
NCT0059302	37	61	0.69	[0.34; 1.42]
Random effects model			**0.66**	**[0.46; 0.96]**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.81				
Random effects model	**770**	**828**	**0.66**	**[0.47; 0.95]**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.94				



Duration of Illness
Subgroup Analysis - ITTI Population

Analysis Subset	Oseltamivir N	Placebo N	Time Ratio (95% CI)	RMST Difference	95% CI
Timing of treatment					
< 24 hours	526	530	0.81 [0.73; 0.90]	−22.8	[−29.43; −16.17]
24−48 hours	244	298	0.93 [0.81; 1.07]	−4.4	[−15.33; 6.53]
Age Group					
< 6 years	357	395	0.82 [0.73; 0.93]	−20.1	[−27.98; −12.22]
6−11 years	290	316	0.87 [0.78; 0.98]	−10.9	[−20.84; −0.96]
12−17 years	71	69	0.71 [0.55; 0.91]	−33.3	[−52.18; −14.42]
Asthma					
Yes	128	148	1.04 [0.86; 1.27]	6.9	[−13.07; 26.87]
No	244	284	0.72 [0.63; 0.81]	−34.9	[−46.38; −23.42]
Influenza Infection Status					
Uninfected	489	428	1.01 [0.90; 1.14]	3.1	[−5.85; 12.05]
Infected	770	828	0.84 [0.77; 0.91]	−17.5	[−23.23; −11.77]



Supplemental material

Pediatric meta-analysis search strategy

PICOS Question: Does treatment with oseltamivir reduce the time to resolution of symptoms in pediatric populations < 18 years old compared to those not receiving treatment?

Additional analyses will answer the PICOS question above for the following outcomes: resolution of fever, disease alleviation without rescue meds, return to normal activity, complications (as defined in MUGAS contract), and safety (occurrence of adverse events [AE] and/or severe adverse events [SAE]).

Population: children (< 18 years old)

Interventions: Oseltamivir within 48 hours of symptom onset

Comparison: Placebo

Outcomes: Time to resolution of illness

Study Design: Randomized clinical trial

We searched PubMed, Medline, EMBASE, and WHO Publications for articles meeting the criteria above. Titles and abstracts were reviewed for all articles identified by these searches.

Search terms (MeSH format):

"Oseltamivir" (preferred MeSH term)

"GS 4071" AND "Influenza, Human"

"GS 4104" AND "Influenza, Human"

"Tamiflu"

Date Range:

1997-May 1, 2016

Restrictions:

English [language]

"Randomized Controlled Trial" [Publication Type]

"Child" OR "Child, Preschool" OR "Adolescent"

((((oseltamivir OR gs 4071 OR gs 4104 OR tamiflu[MeSH Terms])) AND influenza, human[MeSH Terms]) AND (child OR child,preschool OR adolescent[MeSH Terms])) AND randomized controlled trial[Publication Type]

Table S1. Variables requested from trial investigators and whether or not the item was provided

Number	Data	NV16871	WV15758	WV15759/ WV15871	NCT00707941	NCT00593502
1	Study ID	Yes	Yes	Yes	Yes	Yes
2	Unique Identifier	Yes	Yes	Yes	Yes	Yes
3	Age in years	Yes	Yes	Yes	Yes	Yes
4	Sex	Yes	Yes	Yes	Yes	Yes
5	Weight	Yes	Yes	Yes	Yes	Yes
6	Weight for age z-score	No	No	No	Yes	No
7	Treatment indicator	Yes	Yes	Yes	Yes	Yes
8	Date of presentation	Yes	Yes	Yes	Yes	Yes
9	Date of first symptom onset	Yes	Yes	Yes	Yes	Yes
10	Chief complaint	No	No	No	Yes	No
11	Date of chief complaint onset	No	No	No	Yes	No
12	Duration of chief complaint	No	No	No	Yes	No
13	Fever	Yes	Yes	Yes	Yes	Yes
14	Date of fever onset	Yes	Yes	Yes	Yes	Yes
15	Duration of fever	Yes	Yes	Yes	Yes	Yes
16	Temperature	No	No	No	Yes	No
17	Cough	Yes	Yes	Yes	Yes	No
18	Date of cough	Yes	Yes	Yes	Yes	No
19	Runny nose	Yes	Yes	Yes	Yes	No
20	Day of runny nose	Yes	Yes	Yes	Yes	No
21	Loss of appetite	Yes	Yes	Yes	Yes	No
22	Day of loss of appetite	Yes	Yes	Yes	Yes	No
23	Headache	Yes	Yes	Yes	Yes	No
24	Day of headache	Yes	Yes	Yes	Yes	No
25	Body pain	Yes	Yes	Yes	Yes	No
26	Day of body pain	Yes	Yes	Yes	Yes	No
27	Vomiting	Yes	Yes	Yes	Yes	No
28	Day of vomiting	Yes	Yes	Yes	Yes	No
29	Time to return to normal activity	Yes	Yes	Yes	Yes	Yes

30	Time to resolution of illness	Yes	Yes	Yes	Yes	Yes
31	Time to resolution of all symptoms	Yes	Yes	Yes	Yes	Yes
32	Influenza vaccination	Yes	Yes	Yes	Yes	Yes
33	Antibiotic at randomization	Yes	Yes	Yes	Yes	No
34	Antibiotic after randomization	Yes	Yes	Yes	Yes	No
35	Otitis media at baseline	Yes	Yes	Yes	Yes	Yes
36	New onset of otitis media	Yes	Yes	Yes	Yes	Yes
37	Lower respiratory tract illness	Yes	Yes	Yes	Yes -	Yes -
38	Hospitalization	Yes	Yes	Yes	Yes	Yes
39	Time to alleviation of all symptoms	Yes	Yes	Yes	Yes	Yes
40	Rapid test result at baseline	No	No	No	Yes	No
41	Influenza infection status	Yes	Yes	Yes	PCR testing and results on days 0,2,4,7	No
42	Influenza type	Yes	Yes	Yes	Yes	Yes
43	Influenza subtype				Yes	
44	Viral shedding data	Yes	Yes	Yes	TCID 50 and virus culture results on days 0,2,4,7	No
45	Diarrhea	Yes	Yes	Yes	Yes	Yes
46	Duration of diarrhea	Yes	Yes	Yes	Yes	Yes
47	Nausea	Yes	Yes	Yes	Yes	Yes
48	Duration of nausea	Yes	Yes	Yes	Yes	Yes
49	Vomiting	Yes	Yes	Yes	Yes	Yes
50	Duration of vomiting	Yes	Yes	Yes	Yes	Yes
51	Severe adverse event	Yes	Yes	Yes	Yes	Yes

Table S2. Risk of Bias Assessment

Trial	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
NV16871	Low risk	Low risk	Low risk	Low risk	Low risk	NA	Low risk
WV15758	Low risk	Low risk	Low risk	Low risk	Low risk	NA	Low risk
WV15759/ WV15871	Low risk	Low risk	Low risk	Low risk	Low risk	NA	Low risk
NCT00707941	Low risk	Low risk	Low risk	Low risk	Low risk	NA	Low risk
NCT00593502	Low risk	Low risk	Low risk	Low risk	Low risk	NA	Low risk

Time to resolution of illness

Figure S1 shows the duration of illness curves for each trial, by treatment group, for the ITTI population. In two trials (WV15758 and NCT00593502) those in the oseltamivir treatment have a reduced duration of illness. The trials of children with asthma differed in their results. For trial NV16871, there was no evidence of a treatment effect but in trial WV15759/WV15871, there appeared to be a shorter duration of illness for oseltamivir recipients in early follow-up but later in the follow up period the curves converged. Figure S2 shows the duration of illness curves for each trial, by treatment group, for the ITT population. The differences in survival curves are smaller in WV15758 and NCT00593502 as well as for the pooled estimates.

Figure S1. Kaplan Meier curves for duration of illness (hours) in the ITTI population

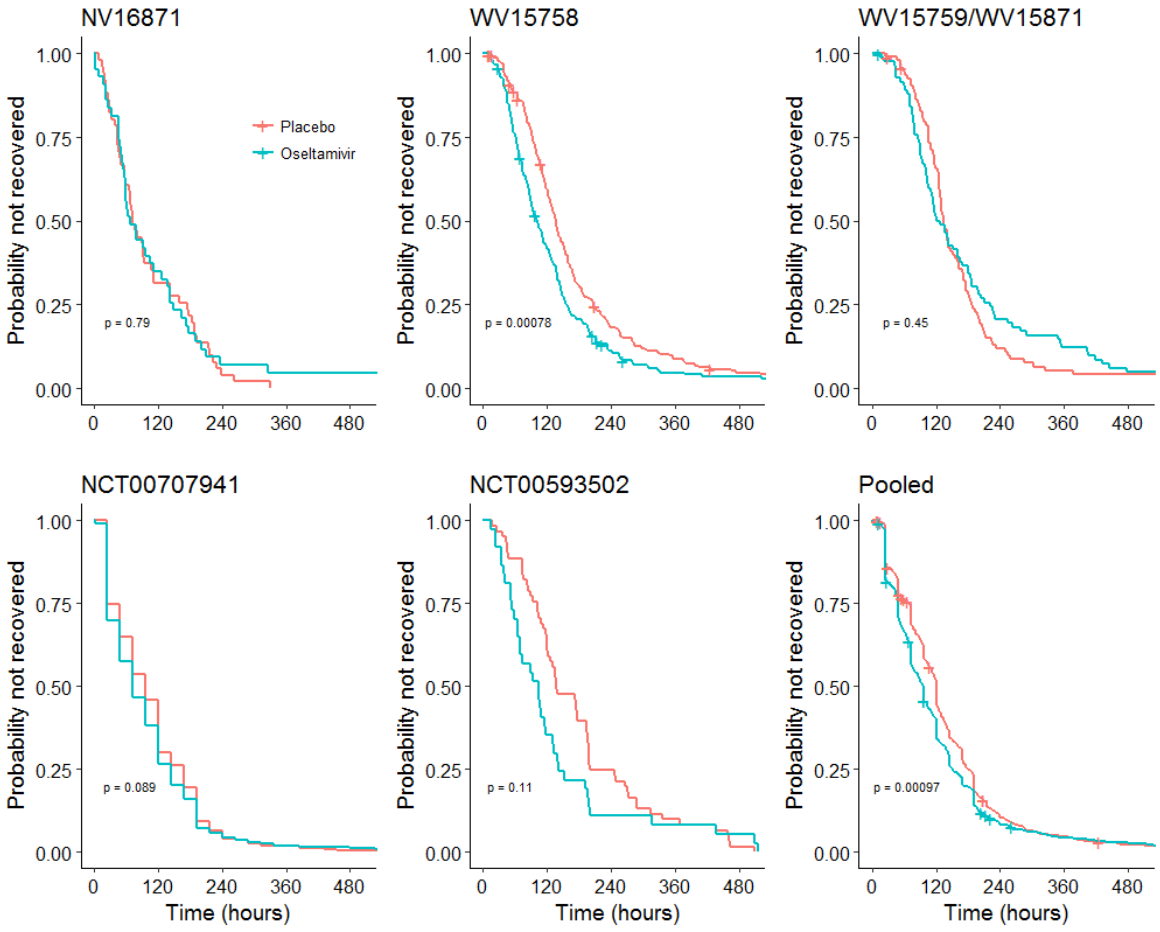


Figure S2. Kaplan Meier curves for duration of illness (hours) in the ITT population

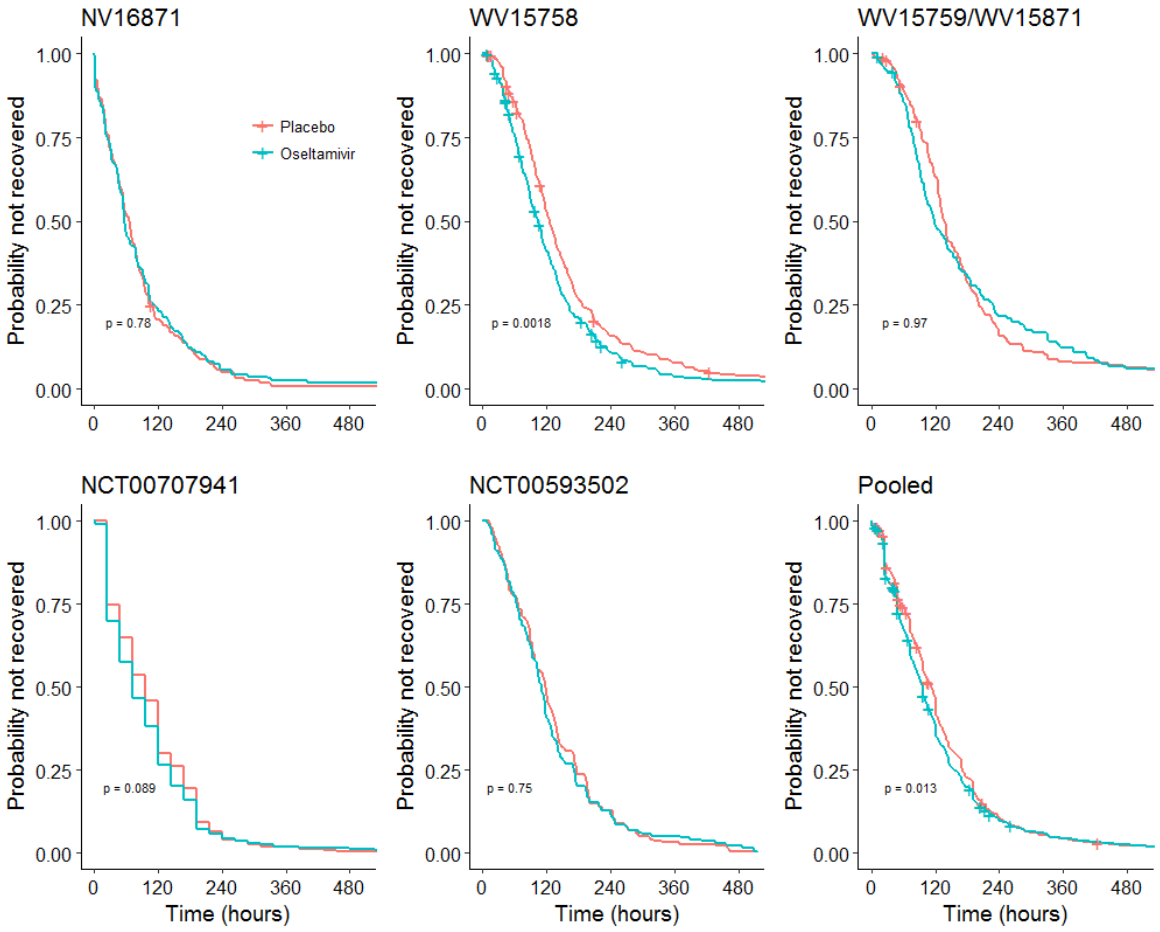


Figure S3. Meta-analysis of time to resolution of illness and time to alleviation of symptoms in the ITT population

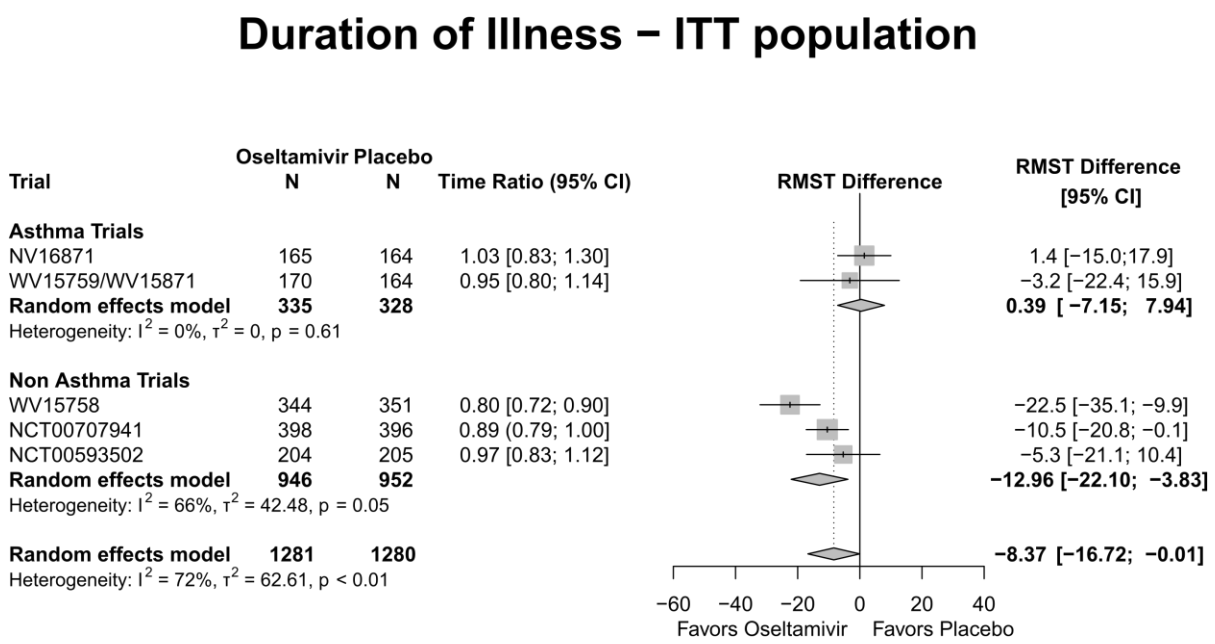


Table S3. Individual patient data analysis, pooled across trials, estimating the relative risk of complications in the ITTI population controlling for potential confounders

	Oseltamivir	Placebo	RR (95% CI)[1]
LRTC	29/770 (3.8%)	38/828 (4.6%)	0.79 (0.48-1.30)
Otitis Media	41/770 (5.3%)	73/828 (8.8%)	0.64 (0.43-0.95)
Hospitalization	4/770 (0.5%)	3/828 (0.4%)	1.12 (0.23-5.54)

[1] RR and 95% CI estimated from log binomial models adjusted for asthma, age group, and trial

Complications – IPD analysis

Table S4. Individual patient data analysis, pooled across trials, estimating the relative risk (RR) of adverse events among 2458 subjects < 18 years old in the safety population

	Oseltamivir	Placebo	RR (95% CI)[1]
Nausea[2]			
Overall	27/1022 (2.6)	28/1030 (2.7)	0.96 (0.57-1.61)
Age Group			
≤ 5	5/408 (1.2)	2/423 (1.6)	2.59 (0.51-13.3)
6-11	17/479 (3.5)	22/477 (4.6)	0.77 (0.42-1.43)
12-17	5/135 (3.7)	4/130 (3.1)	1.31 (0.36-4.75)
Influenza infected[2]	17/689 (2.5)	23/730 (3.2)	0.81 (0.44-1.50)
Influenza uninfected	10/333 (3.0)	5/300 (1.7)	1.82 (0.64-5.19)
Vomiting			
Overall	170/1224 (13.9)	104/1234 (8.4)	1.65 (1.31-2.06)
Age Group			
≤ 5	93/610 (15.2)	68/627 (10.8)	1.41 (1.06-1.87)
6-11	69/479 (14.4)	33/477 (6.9)	2.09 (1.41-3.10)
12-17	8/135 (5.9)	3/130 (2.3)	2.25 (0.61-8.35)
Influenza infected	76/727 (10.5)	63/794 (7.9)	1.42 (1.04-1.97)
Influenza uninfected	94/497 (18.9)	41/440 (9.3)	1.97 (1.41-2.75)
Diarrhea			
Overall	147/1224 (12.0)	166/1234 (13.5)	0.91 (0.75-1.10)
Age Group			
≤ 5	122/610 (20.0)	136/627 (21.7)	0.93 (0.75-1.14)
6-11	19/479 (4.0)	28/477 (5.9)	0.68 (0.39-1.20)
12-17	6/135 (4.4)	2/130 (1.5)	2.36 (0.49-11.36)
Influenza infected	71/727 (9.8)	104/794 (13.1)	0.79 (0.60-1.04)
Influenza uninfected	76/497 (15.3)	62/440 (14.1)	1.05 (0.79-1.38)
Severe Adverse Events [2,3]			
Overall	11/1022 (1.1)	4/1030 (0.4)	2.67 (0.85-8.35)
Age Group			
≤ 5	5/408 (1.2)	1/423 (0.2)	5.21 (0.61-44.39)
6-11	4/479 (0.8)	3/477 (0.6)	1.37 (0.31-6.06)
12-17	2/135 (1.5)	0/130 (0.0)	--
Influenza infected	4/689 (0.5)	2/730 (0.3)	2.07 (0.34-11.29)
Influenza uninfected	7/333 (2.1)	2/300 (0.7)	2.97 (0.62-14.15)

[1] Overall and influenza stratified models estimate the RR and 95% CI from log binomial models adjusted for trial and age group; Age stratified models estimate the RR and 95% CI from log binomial models adjusted for trial.

[2] Trial NCT00593502 did not collect data on Nausea or Severe Adverse Events so these data are excluded from this analysis

[3] 0 SAEs in placebo recipients 12-17 years old, therefore RR cannot be calculated

Table S5. Pooled difference in RMST from meta-analysis including all trials, and excluding specific trials. Overall estimate and stratified estimates by inclusion of only children with asthma.

		Excluding				
	Pooled Estimate	NV16871	WV15758	WV15759/ WV15871	NCT00707941	NCT00593502
Overall	-17.6	-22.1	-11.3	-22.4	-20.0	-12.2
Asthma	2.2	3.7	2.2	0.9	2.2	2.2
Non-asthma	-29.9	-29.9	-26.3	-29.9	-40.2	-23.7

Sensitivity of estimates to definition of laboratory confirmed influenza

Some have suggested that the ITTI population may be biased because serologic confirmation of infection would underestimate the number of infected individuals. This may be true generally in populations with high levels of underlying immunity (e.g. highly vaccinated) or in those who are unlikely to shed enough virus for culture (adults). Given that only 8% of the children in the included studies received the current season vaccine and that this number was closely balanced by treatment group, we do not think our results are likely to be affected by this bias. Nevertheless we conducted a sensitivity analysis excluding influenza cases identified by rise in serum antibody titer alone (n=74, 0.9%). RMST difference and time ratios were similar to those for the ITTI population

Figure S4. Sensitivity analysis excluding serologic confirmation of infection from the ITTI population