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

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(See the Editorial Commentary by Uyeki on pages 1501–3.)

Background. Oseltamivir has been used to treat children with influenza for nearly 2 decades, with treatment currently approved for infants aged ≥2 weeks. However, efficacy and safety remain controversial. Newer randomized, placebo-controlled trials (RCTs), 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 2-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 (RMST) by treatment group. We also examined complications and safety.

Results. We identified 5 trials that included 2561 patients in the intention-to-treat (ITT) and 1598 in the intention-to-treat infected (ITTI) populations. Overall, oseltamivir treatment significantly reduced the duration of illness in the ITTI population (RMST difference, −17.6 hours; 95% confidence interval [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.

Conclusions. 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.

Keywords. influenza; oseltamivir; children; meta-analysis.

Globally, influenza is an important contributing cause of hospitalization and mortality in children aged <5 years [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 US Food and Drug Administration in 1999 for treatment of uncomplicated influenza. The results of the pivotal licensure studies [5–7] were remarkably similar, even though the 2 drugs were dissimilar in their mode of administration and metabolism. In the nearly 2 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 as young as 2 weeks [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, placebo-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 aged <18 years. Following a systematic review that identified 2 recently published trials, we estimated the efficacy of timely oseltamivir

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treatment for uncomplicated influenza by comparing children treated in the outpatient setting to those who received placebo.

METHODS

Systematic Review

We searched PubMed, MEDLINE, Embase, and the Cochrane Library for clinical trials published between 1 January 1997 and 1 May 2016 using medical subject heading terms to identify oseltamivir studies in children with influenza virus infection. Unique titles and abstracts were reviewed for eligibility using prespecified Population, Intervention, Comparator, Outcome, Study design (PICOS) criteria (Figure 1). Nonprimary literature that included reviews, meta-analyses, or secondary analyses were excluded. We reviewed reference lists of systematic reviews and previous meta-analyses and contacted investigators to identify additional trials. Data were obtained from Roche via the Multiparty Group for Advice on Science for 2 published (WV15758 and WV15759/WV15871) and 1 unpublished trial (NV16871); data from 2 additional trials (NCT00707941 and NCT00593502) were obtained directly from investigators (Supplementary Table S1). The risk of bias was evaluated using the Cochrane tool to describe the data quality from each trial (Supplementary Table S2). The protocol for this systematic review was registered with PROSPERO (14 July 2016; 42016038982) prior to initiation of the review.

Meta-analysis

We conducted a 2-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 (Supplementary Figures S1 and S2). Treatment effect estimates (time ratio) by trial were obtained from an accelerated failure time 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 (CIs) were also estimated for each trial individually [22]. We then conducted a random-effects meta-analysis with a maximum likelihood approach to estimate heterogeneity between trials. All analyses were performed using R version 3.3.2.

Efficacy analyses were first restricted to patients who received at least 1 dose of study drug and who had laboratory-confirmed influenza virus infection (intention-to-treat infected [ITTI] 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

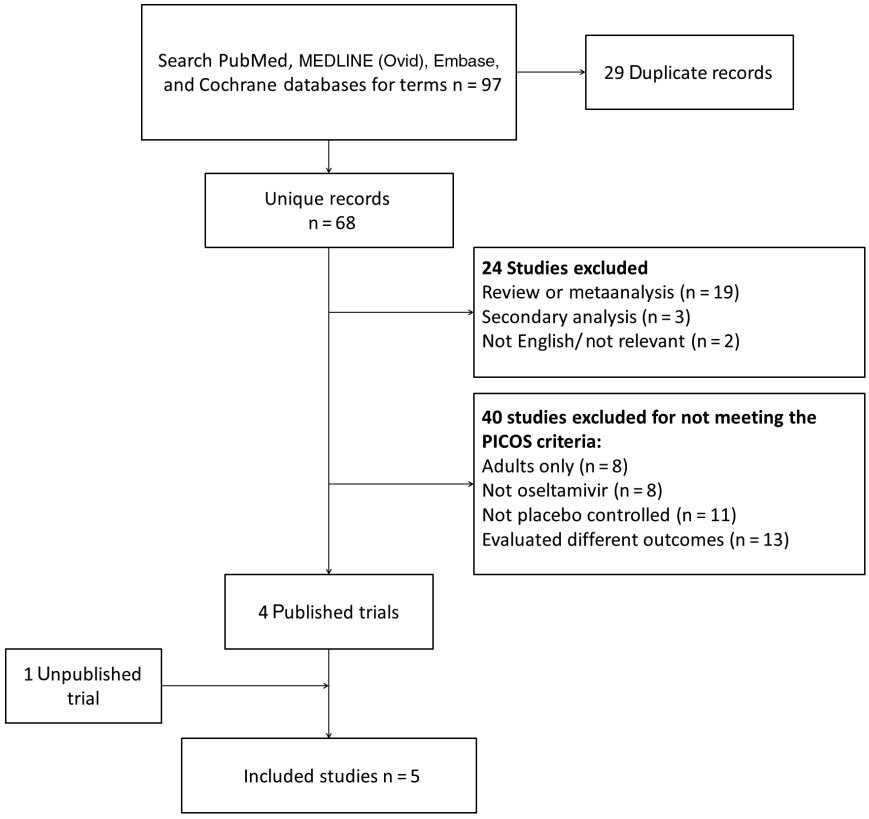

Figure 1. Results of the systematic review. Abbreviation: PICOS, Population, Intervention, Comparator, Outcome, Study design.

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: 3 trials (WV15759/WV15871, WV15758, and NCT0059302) used the phrase "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 (eg, fever, tachypnea, difficult/noisy breathing, cough, and any danger sign; NCT00707941).

Complications and Adverse Events

Binary outcomes (eg, complications, adverse events) were also analyzed using a 2-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. Patients who took 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 (SAEs) 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 Analyses

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 who received treatment early (ie, 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 Materials) 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 1 additional unpublished trial; thus 5 trials were included in the final analysis.

Description of Trials and Participant Characteristics

Three trials (WV15758 [24], WV15759/WV15871 [25], and 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 had at least 1 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 and included only participants aged <4 years who presented 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 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, 796 of whom were included in this meta-analysis because they were randomized within 48 hours of symptom onset. A total of 394 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, 46 (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 who received 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 = .03), indicating heterogeneity between asthma-only and combined populations. Thus, we stratified the meta-analysis based on trial inclusion criteria in regard to asthma status. The effect of treatment was larger in trials that enrolled children regardless of asthma status (RMST difference −29.9 hours;

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 (1–12 y) <48 h of symptom onset	Children with asthma (≥6 y–≤12 y) <48h of symptom onset	Children with asthma (≥6 y–≤17 y) <48 h of symptom onset	Age +1y, no upper age limit (89% <18 y, ~80% ≤10y) within 5 days symptom onset	Children (1–3 y), early treatment (≤24 h of symptom onset)
Location	United States, Canada	Europe, Israel, United States, Canada, Argentina, Australia, Chile, China, New Zealand, South Africa	Europe, Israel	Bangladesh	Finland
Numbers of intention-to-treat patients	695 (planned = 680)	334 (planned = 500)	329 (planned = 392)	796 (<48 h from onset)[a]	408 (planned = 308)
Number (%) intention-to-treat infected 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 (<48 h from onset)[a] -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 <48 h 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 from 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

Abbreviation: RT-PCR, real-time polymerase chain reaction.

Overall 1190 patients enrolled and randomized, 796 patients randomized <48 hours from onset eligible for inclusion in meta-analysis. Separate randomization for those enrolled >48 hours from onset.

95% CI, −53.9 to −5.8 hours). For trials that enrolled only patients with asthma, there was no effect of treatment (Figure 2). Reductions in the duration of illness were attenuated in the ITT population (Supplementary Figure S2) but remained significant (RMST difference, 8.4 hours; 95% CI, −16.7 to −0.01 hours; Supplementary Figure S3).

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%]; relative risk [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 with complete data on complications (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 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 SAEs among 2558 patients in the safety population (Table 3). SAEs 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 = ·93) and withdrawal due to an adverse event (8/676 [1%] vs 8/682 [1%]; P = ·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 hours, 95% CI,−15.5 to 6.5 hours). We observed the largest reduction

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, y (%)						
≤ 5	197 (56.1)	193 (56.1)	0 (0.0)	0 (0.0)	2 (1.2)	4 (2.4)
6–11	138 (39.3)	139 (40.4)	90 (54.9)	93 (56.4)	151 (92.1)	145 (85.3)
12–17	16 (4.6)	12 (3.5)	74 (45.1)	72 (43.6)	11 (6.7)	21 (12.4)
≥18	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 (100.0)	398 (100.0)	61 (29.8)	37 (18.1)	828 (65.5)	770 (60.8)	
Age category, y (%)							
≤ 5	222 (56.1)	213 (53.5)	205 (100.0)	204 (100.0)	626 (48.9)	614 (47.9)	0.927
6–11	98 (24.7)	102 (25.6)	0 (0.0)	0 (0.0)	477 (37.3)	479 (37.4)	
12–17	28 (7.1)	31 (7.8)	0 (0.0)	0 (0.0)	129 (10.1)	136 (10.6)	
≥18	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

Abbreviations: ITT, intention-to-treat; ITTI, intention-to-treat infected.

in duration of illness among adolescents (aged 12–17 years), though CIs 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

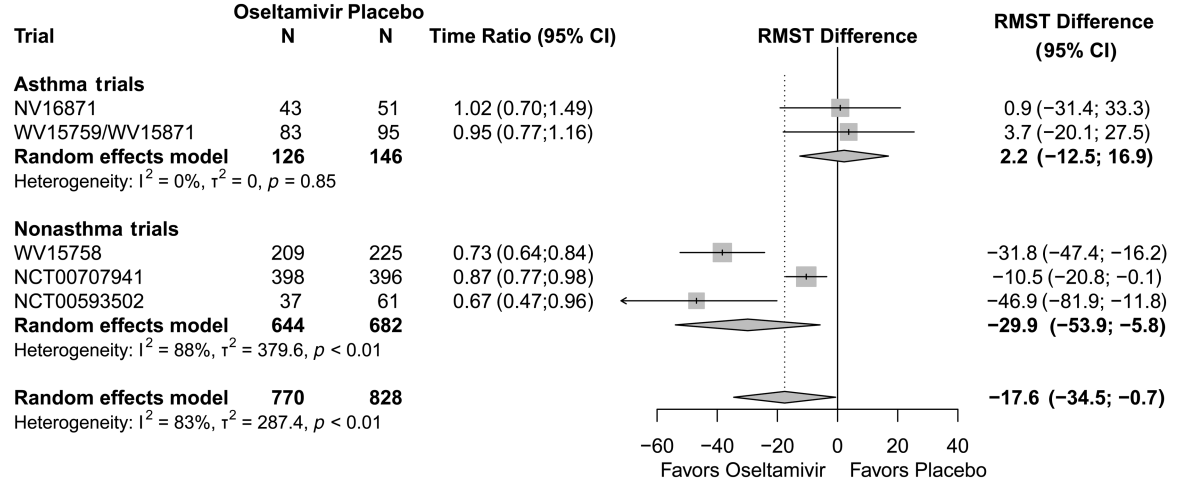

Figure 2. Forest plot, random-effects meta-analysis of the efficacy of oseltamivir treatment in reducing duration of illness as measured by the difference in restricted mean survival time and time ratio from accelerated failure time models in the intent-to-treat infected population. Abbreviations: CI, confidence interval; RMST, restricted mean survival time.

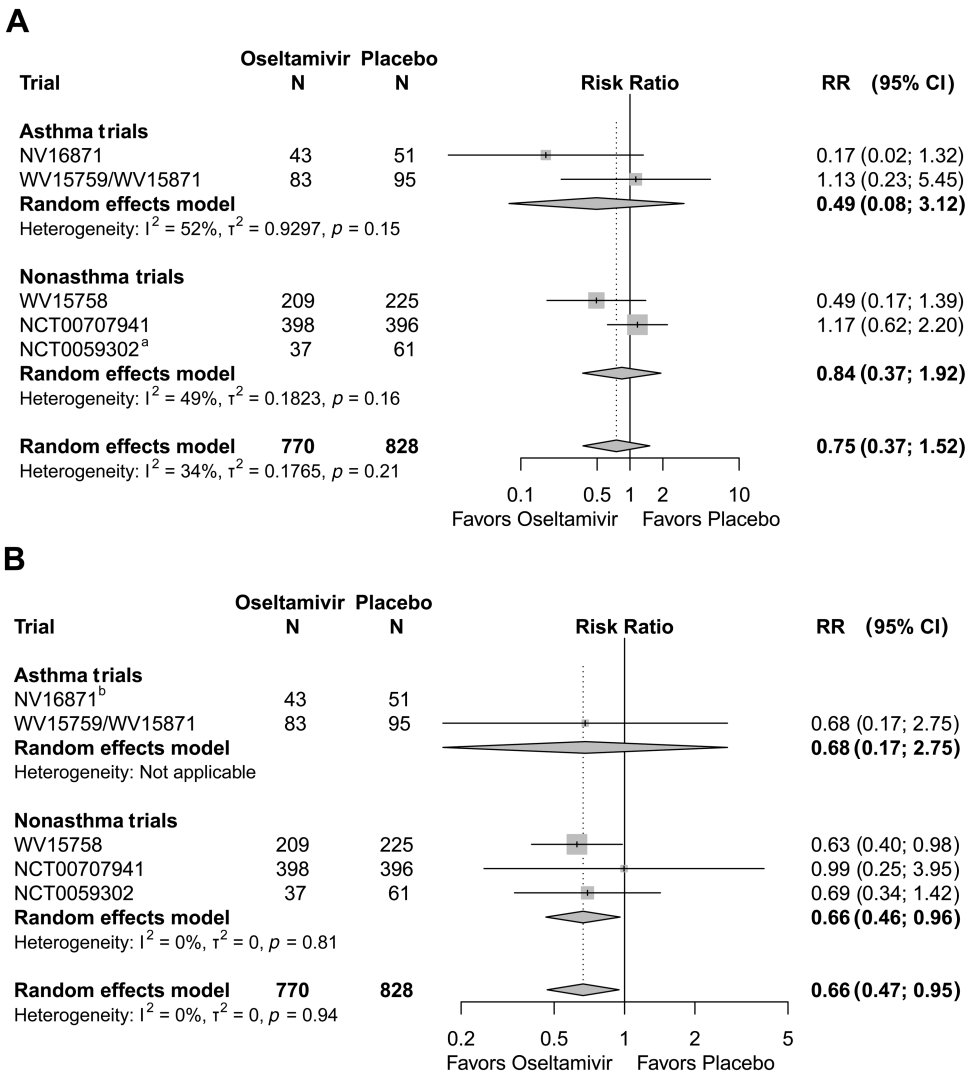

Figure 3. Forest plot, random-effects meta-analysis of the relative risk of developing complications in the intent-to-treat infected population. *(A)* Lower respiratory tract complications and *(B)* otitis media. Relative risk estimated from log-binomial regression models. Abbreviations: CI, confidence interval; RR, relative risk.

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, were similar to the meta-analyses described above for both complications (Supplementary Table S3) and safety outcomes (Supplementary Table S4).

DISCUSSION

In the current analysis, we demonstrated a reduction in the duration of illness of approximately 18 hours among children who received timely oseltamivir treatment compared to placebo. In addition, we found that treatment reduced the risk of otitis media

Table 3. Meta-analysis of Adverse Event Outcomes

Study	Placebo N	Oseltamivir N	Relative Risk[a] (95% Confidence Interval)			
			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)

[a]Relative risk estimated from log-binomial regression models.

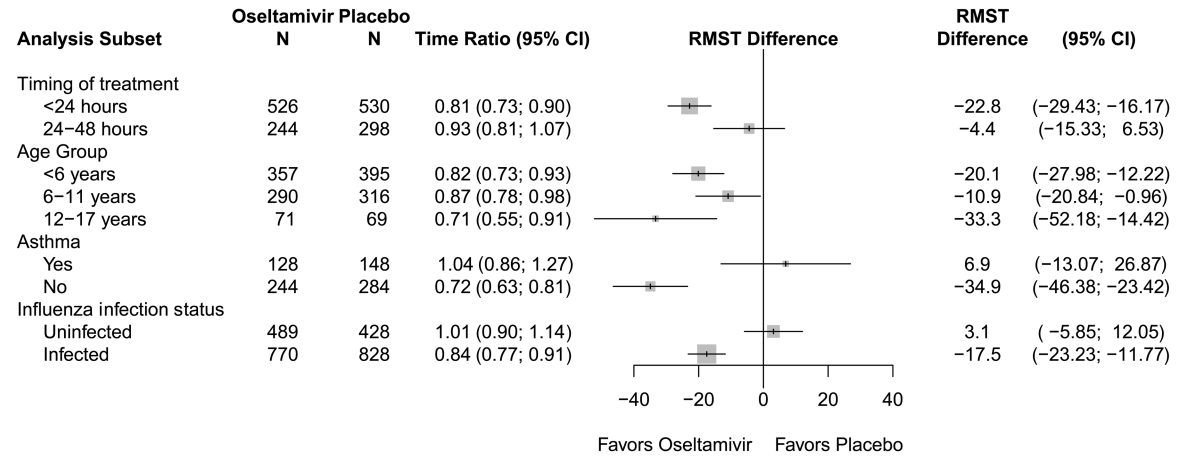

Figure 4. Forest plot, pooled analysis estimating the time ratio from accelerated failure time models with generalized F distribution and restricted mean survival time difference and 95% confidence interval for patients who received oseltamivir compared to placebo stratified by subgroups of interest and controlling for trial. Abbreviations: CI, confidence interval; RMST, restricted mean survival time.

and that there was little evidence of safety issues, except for 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 works, were all conducted around the time of licensure. The study populations varied in some trials (eg, older adults or those with underlying conditions), but all trials used a similar endpoint, referred to as "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 under 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 that would require clinical referral [27]. Two other trials included only children with asthma, one limited to children aged >6 years, and each used a different primary endpoint. To address this heterogeneity, we performed a random-effects meta-analysis and used the outcome that 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 (Supplementary Table S5). 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 when the Bangladesh trial was included 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 antiinflammatory 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 (Supplementary Figure S4).

The major outliers in this analysis were the trials that included only children with asthma. The pooled estimate for the 3 trials that did not specifically enroll asthma patients was a reduction in illness duration of 29.9 hours, which is 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 recognizing clinical illness endpoints in those with underlying respiratory conditions. Alternate endpoints such as improvement 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 SAEs but did detect an increase in the risk of vomiting in those who received 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, which resulted in approval in the United States for children aged as young as 2 weeks [9, 33]. In these studies, vomiting was also the only adverse effect seen more often with oseltamivir compared with placebo [9]. Approval was an explicit recognition of the need for an antiviral to treat influenza virus infections in this vulnerable population.

Reduction in 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 who received oseltamivir treatment. Similar reductions have been found in individual studies [24, 28] and in the pivotal evaluations of live attenuated influenza vaccine in children aged <6 years [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 in that, for uncomplicated influenza, oseltamivir appears to be as safe and effective in children as in 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. R. J. W. reports receipt of fees as a board member of Gilead Sciences. A. S. M. reports receipt of consulting fees from Roche related to the submitted work and from Seqirus outside the submitted work. All remaining authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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