Neuraminidase inhibitors are effective and safe in reducing influenza complications: meta-analysis of randomized controlled trials.

Authors: Sofía Tejada[1,2*], Miia Jansson[3], Candela Solé-Lleonard[4], Jordi Rello[1,2,5]

Affiliations

[1] CIBER de Enfermedades Respiratorias, CIBERES, Instituo Salud Carlos III, Barcelona, Spain

[2] Clinical Research/Epidemiology in Pneumonia & Sepsis (CRIPS), Vall d'Hebron Institut of Research (VHIR), Barcelona, Spain

[3] University of Oulu, Oulu University Hospital, Oulu, Finland

[4] Intensive Care Unit, Hospital Universitario de Vic, Barcelona, Spain

[5] Clinical Research in the ICU, Anesthesia Department, CHU Nimes, Universite de Nimes-Montpellier, France

Manuscript words:

***Corresponding author**

Sofía Tejada

Vall d'Hebron Institut de Recerca

Ps Vall d'Hebron 119 AMI-14th floor. 08035 Barcelona, Spain

Email address: stmagraner@gmail.com

The final authenticated version is available online at https://doi.org/10.1016/j.ejim.2020.12.010

Abstract (words: 250)

Background: There is scarce evidence verifying the impact of neuraminidase inhibitors (NAIs) in reducing influenza complications. The aim of the study was to evaluate the effectiveness and safety of NAIs in reducing influenza complications, by performing a meta-analysis of the relevant randomized controlled trials (RCTs).

Methods: The Cochrane collaboration searching methods was followed in Cochrane Library, PubMed and Web of Science databases (2006–2019). Eligibility criteria were RCT that enrolled patients of any age or health status with seasonal influenza (H_1N_1, H_3N_2, or B) or influenza-like syndrome and receiving NAIs comparing to placebo therapy.

Results: Eighteen RCTs (9004 patients) were included: nine focused on oral oseltamivir therapy, six on inhaled zanamivir, and three on intravenous peramivir. Time to clinical resolution and total influenza-related complications were significantly less in patients treated with NAIs vs placebo (10 RCTs, OR: -17.78 hours, 95% CI: -26.78 to -8.79 and 11 RCTs, OR: 0.64, 95% CI: 0.51–0.82, respectively). Effectiveness of NAIs in reducing total influenza-related complications in patients with confirmed influenza infection was more pronounced in high-risk patients (2 RCTs, 106 patients, OR: 0.22, 95%CI: 0.09–0.55), p <0.05 for the test for χ^2 subgroup differences. A trend to lower complications was observed improvements in other efficacy outcomes with NAIs. No significant difference was reported in the occurrence of total drug-related adverse events between patients treated with NAIs vs placebo (7 RCTs, 3099 patients, OR: 1.06, 95% CI: 0.86–1.31).

Conclusions: NAIs comparison to placebo did demonstrate to be effective and safe in reducing time to clinical resolution and total influenza-related complications.

Keywords: influenza, neuraminidase inhibitors, oseltamivir, zanamivir, peramivir, complications.

Formatted: Font: Italic

Introduction

Influenza is an infection of variable severity result with high accumulated mortality worldwide[1]. Seasonal influenza deaths occur mainly in young children and the elderly, while during influenza pandemics, young adult individuals are more affected[2,3]. Influenza vaccination is the primary method for preventing influenza and reducing the risk of severe outcomes, but in many scenarios, thanks to its high rate of genetic drift, the result is suboptimal[4,5]. However, the treatment for influenza infection is near limited to neuraminidase inhibitors (NAIs) due to the rapid occurrence of resistance to M2 inhibitors (amantadine and rimantadine) observed during the last influenza pandemic in 2009[6].

The World Health Organization (WHO) and the European Centre for Disease Control (ECDC) recommend the use of NAIs for influenza adults[7]. The Infectious Diseases Society of America (IDSA) released guidelines on influenza management in 2018, identifying NAIs as first-line therapy, with no differences between oral oseltamivir, intravenous peramivir, or inhaled zanamivir[8]. Although a considerable number of studies indicate the effectiveness and safety of NAIs administration in reducing the severity and the length of influenza illness[9–12], there is scarce evidence verifying their impact on preventing and treating of serious complications (such as pneumonia, bronchiolitis, sinusitis, otitis media)[13–15]. A study in 2009[16] reported reducing complications with seasonal influenza A(H_1N_1) or A(H_3N_2). However, the other introduction of influenza A(H_1N_1)pdm09 the effects remaining unknown.

The hypothesis was that the treatment with ~~neuraminidase inhibitors~~NAIs reduced the influenza complications in patients with influenza (H_1N_1, H_3N_2, or B). The study's aim was to evaluate the effectiveness and safety of NAIs, used for the treatment of influenza, in reducing influenza complications, by performing a meta-analysis of the relevant randomized controlled trials (RCTs).

Methods

Protocol and Registration

This report describes the results of the systematic review and meta-analyses following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[17]. The protocol was published in the National Institute for Health Research international prospective register of systematic reviews (PROSPERO); registration number: CRD42020172080.

Data sources

A global search strategy was systematically performed in three databases: MEDLINE database through the PubMed search engine, the Cochrane Library Database and Web of Science database. Websites from ClinicalTrials.gov and clinicaltrialsregister.eu were consulted for other ongoing trials. Search terms were detailed in additional ~~file~~ File 1. Restrictions in the search were applied regarding the language: only studies published in English, French and/or Spanish were considered. Abstracts presented at scientific conferences, unpublished studies, or other unpublished data deriving from industry sites were excluded. No restriction was applied to the publication period of time. The search was performed in December 2019.

Data extraction and study selection process

Two authors (ST and CSL) independently evaluated all the studies identified in the literature search by screening their titles, abstracts, and full-text. In case of disagreement, a third author (JR) independently determined eligibility. Data were extracted by the corresponding author; meanwhile, the extracted data was crosschecked by another author (MJ). A predesigned spreadsheet to collect study data in a standardized way was used. Data extracted from each trial included ~~were~~ the study design, quality assessment, characteristics of the study populations, laboratory method used for confirmation of the influenza infection, characteristics of compared treatment arms and potential concomitant treatment, the types of influenza complications and adverse events evaluated, the intention to treat (ITT) population and the subgroup of patients with laboratory-confirmed influenza infection, the time-points of follow-up assessments, as well as data regarding the effectiveness and safety outcomes. Only patient-related data were included.

Studies were considered eligible for inclusion in the meta-analysis if they represented an RCT that enrolled patients of any age or health status with seasonal influenza (H_1N_1, H_3N_2, or B) or influenza-like syndrome and receiving either antiviral treatment (NAIs) or placebo. Pre-defined NAIs were oseltamivir (oral

administration), zanamivir (inhaled administration), and peramivir (intravenous administration). Additionally, the trials should have provided data regarding any influenza complication of interest.

Definitions and outcomes

Clinically suspected influenza was defined by the presence of respiratory symptoms (sore throat, cough, headache, muscle or joint aches and pains) for more than 48 hours and fever (≥37.7ºC). The ITT population included all patients randomized to receive the respective study regimens. The influenza-confirmed population was defined by the presence of a positive polymerase-chain-reaction (PCR), viral culture, immunofluorescence assay or rapid antigen test (RAT) for influenza virus. High-risk patients were patients with chronic respiratory disease (asthma, chronic obstructive pulmonary disease) requiring regular medication, or chronic cardiac disease (excluding hypertension), immunocompromised or elderly individuals (>65 years). Studies meeting the inclusion criteria that reported at least one statistical comparison between the intervention and comparators were included. The definitions were defined elsewhere[16].

The time to clinical resolution (TTCR), defined by the individual study protocol as the time from initiation of the study treatment until resolution of vital sign abnormalities; and total influenza-related complications, defined as any pre-defined complication (pneumonia, bronchitis, asthma exacerbations, otitis media, sinusitis and pharyngitis) occurring at any time during the study, were considered as the primary effectiveness outcomes of this meta-analysis. Other effectiveness and safety outcomes were defined elsewhere[16].

Quality assessment

Risk of bias was assessed for each included study independently by two reviewers (ST and CSL) based on the Cochrane Handbook of SR of Interventions[18] and using the Cochrane Review Manager 5.3 risk of bias tool which takes account of allocation sequence generation, concealment of allocation, masking of participants and investigators, incomplete outcome reporting, selective outcome reporting, or other sources of bias. Each potential source of bias was graded to determine whether studies were considered at high, low, or moderate risk of bias. In case of disagreement, a third author (JR) independently determined the quality assessments.

Data analysis

For categorical outcomes, the number of patients who had each outcome and denominator were extracted, and for continuous outcomes, sample size, mean [standard deviation (SD)] or median [~~Interquartil~~Interquartile Range (IQR)] were extracted, based on the information provided within studies. Where results were not reported in a format suitable for meta-analysis we used recommended methods from the Cochrane collaboration to extract or estimate effects including contacting study authors and using formulae to conversion of medians (IQR) to estimated mean (SD) as previously described[19].

The meta-analysis was performed when sufficient data for each outcome were reported. All statistical analyses were performed using Review Manager (RevMan) version 5.3. The summary statistic measures used for the evaluation of dichotomous outcomes were the odds ratio (OR). Continuous outcomes are presented as mean differences. All statistical measures were calculated with 95% Confidence Interval (CI). Random-effects meta-analysis using the Mantel–Haenszel model approach was chosen to obtain pooled study results. The Higgins I^2 test was used to describe heterogeneity between studies ($I^2 \leq 25\%$ for low, $25\% < I^2 < 50\%$ for moderate, $I^2 \geq 50\%$ for high).

Commented [MJ1]: Should we include the interpretation of results? And P-value?

Results

A total of 4613 studies were identified: 6323 studies in the MEDLINE (PubMed), 869 in Web of Science, and 421 in the Cochrane Library databases. Of these, 18 studies were eligible for inclusion. The PRISMA flow diagram of the studies' selection is presented in additional file 2. A summary of their risk of bias of the included RCT is detailed in figure 1.

Interventions

A total of 18 trials[20–37] was included in the study. Nine trials focused on oral oseltamivir therapy twice/daily for 5 days: four trials[20–22,24] administered 75mg; two trials[25,26] administered 2mg/kg; one trial[23] administered between 30-45mg depending on the weight; and two trials[27,28] administered 75 or 150 mg. Six trials focused on inhaled zanamivir therapy twice/daily for 5 days: five trials[29–33] administered 10mg; one trial[34] administered 10 mg plus zanamivir intranasal spray (6.4 mg) or plus placebo nasal spray. Three trials focused on intravenous peramivir once/daily for 5 days: one trial[35] administered 600mg; one trial[36] administered 150 or 300 mg; one trial[37] administered 300 or 600mg. Placebo was administered as a comparator twice/daily (oral oseltamivir or inhaled zanamivir) or once/daily (intravenous peramivir). Main characteristics of the trials included studies are described in table 1.

Population

A total of 9004 patients were included in the 18 analyzed trials. Of these, 6258 (69.5%) had confirmed influenza infection, and 283 (3.1%) were vaccinated against influenza. Baseline characteristics of the population included are described in table 2. Twelve trials[20,22,24,27–29,31–34,36,37] involved patients aged less than or equal to 12 years ~~only patients (≥12 year)~~, whereas the remaining five trials[21,23,25,26,30] involved children (<12 years old) and one trial[35] involved adults (≥ 18 years), adolescents (11-12 years), or children (6-11 years) ~~old~~. A total of 463 (5.1%) patients received any antibiotic treatment and 511 (5.6%) patients reported any complication at baseline.

Outcomes

Studies meeting the inclusion criteria that reported at least one statistical comparison between the intervention and comparators were included. Trials included for each outcome included in the meta-analysis is reported in additional file 3.

Effectiveness outcomes

Studies with two kinds of intervention, the standard of care of each NAI (75mg oral oseltamivir twice/daily, 10mg inhaled zanamivir twice/daily, or 600mg intravenous peramivir once/daily) were eligible for the meta-analysis. The mean TTCR was significantly less ~~likely TTCR~~ in patients treated with NAIs vs placebo (10 RCTs, 2848 patients, OR: -17.78 hours, 95% CI: -26.78 to -8.79) with a high degree of heterogeneity (I^2=100%). The meta-analysis of TTCR is presented in figure 2. When considering the three groups of NAIs, the average TTCR was significantly lesser in patients treated with oseltamivir vs. placebo ~~we found a significantly less likely TTCR in patients only treated with oseltamivir vs placebo~~ (7 RCTs, 2359 patients, OR: -23.23 hours, 95% CI: -35.33 to -11.13) and in patients treated with zanamivir vs placebo (1 RCTs, 174 patients, OR: -0.90 hours, 95% CI: -1.73 to -0.07).

The total influenza-related complications were significantly less likely in patients treated with NAIs vs placebo (11 RCTs, 3710, OR: 0.64, 95% CI 0.51–0.82) with a moderate degree of heterogeneity (I^2=35%). The meta-analysis of total influenza-related complications in laboratory-confirmed influenza patients treated with oseltamivir, zanamivir, or peramivir compared with placebo is presented in figure 3A. When considering the three groups of NAIs, ~~assessed in the studies included in the meta-analysis, we reported a significantly less likely~~the total influenza-related complications were lesser in patients ~~only~~ treated with oseltamivir vs, placebo (4 RCTs, 1357 patients, OR: 0.51, 95% CI: 0.30–0.89) and in patients treated with zanamivir vs placebo (5 RCTs, 1633 patients, OR: 0.71, 95%CI: 0.52–0.98).

Although the effectiveness of NAIs in reducing total influenza-related complications reported a significant decrease in all patients with confirmed influenza infection, it was more pronounced in high-risk patients (2 RCTs, 106 patients, OR: 0.22, 95% CI: 0.09–0.55). The meta-analysis of total influenza-related complications in laboratory-confirmed influenza patients, as well as high-risk patients that were treated with NAIs compared with placebo is presented in figure 3B. Likewise, the effectiveness of NAIs in reducing total influenza-related complications with confirmed influenza infection is less in both adults and pediatric patients (11 RCT, 3309 patients, OR: 0.62, CI ~~IC~~95%: 0.49-0.80). The meta-analysis of total influenza-related complications in pediatric and adult patients with laboratory-confirmed influenza is presented in figure 3C.

A trend to lower complications was observed improvements in other efficacy outcomes with NAIs and the meta-analysis are reported in table 3 and additional file 4. The pneumonia and bronchitis complications were not reported difference in patients treated with NAIs vs placebo (5 RCTs, 1923 patients, OR: 0.44, 95% CI 0.10–2.00 and 5 RCTs, 1767 patients, OR: 0.80, 95% CI 0.43–1.48, respectively). The acute otitis media complication was significantly less likely in patients treated with NAIs vs placebo (6 RCTs, 2119 patients, OR: 0.50, 95% CI 0.31–0.82) with a low degree of heterogeneity (I^2=0%). Interestingly, we reported a significantly less likely in pediatric patients (2 RCTs, 481 patients, OR: 0.49, 95% CI: 0.29–0.83).

Commented [MJ2]: Should we say this in the way of:

Commented [MJ3]: Do you mean significantly less acute otitis in pediatric patients? Rewrote, please

Five of eighteen included studies provided pharyngitis/tonsillitis, and only one of these, provided pharyngitis/tonsillitis in confirmed influenza infection patients. Out of eighteen included studies, seven provided mortality. Only three deaths occurred in patients assigned to the placebo treatment arm vs. intravenous peramivir.

Safety outcomes

No significant difference was reported in the occurrence of total drug-related AEs between patients treated with NAIs vs placebo (7 RCTs, 3099 patients, OR: 1.06, 95% CI: 0.86–1.31). The meta-analysis of total drug-related AEs is presented in figure 4. Also, no difference trend was reported in the occurrence of nausea/vomiting (10 RCTs, 4639 patients, OR: 1.47, 95% CI: 0.91–2.36) or diarrhea (10 RCTs, 5036 patients, OR: 0.81, 95% CI: 0.65–1.00) between patients treated with NAIs vs placebo. The results suggest that nausea/vomiting was causing by NAIs whereas diarrhea was by viral origin.

Regarding study withdrawals due to ~~adverse events~~AEs, no difference was found between patients treated with NAIs vs placebo (12 RCTs, 5109 patients, OR: 1.11, 95% CI: 0.69–1.79). The meta-analysis of study withdrawals due to adverse events is presented in additional file 4.

Discussion

A systematic literature review was undertaken to evaluate the effectiveness and safety of NAIs in reducing influenza complications of patients with influenza. According to our findings, the mean TTCR and the total number of influenza-related complications were significantly less in patients treated with NAIs (e.g., oseltamivir and zanamivir) vs. placebo, while no significant difference was reported in the occurrence of total drug-related AEs between patients treated with NAIs vs. placebo.

Contrary to previous literature, we included not only oseltamivir and zanamivir, but also peramivir. According to our results, however, the mean TTCR and the total influenza-related complications were significantly less likely in patients treated with oseltamivir and zanamivir, but not with peramivir. This may be due to the limited number of analyzed trials included in the respective comparisons. In literature, the time to alleviation of symptoms or fever has been lower in the peramivir-treated group compared with the oseltamivir-treated group[41,42]. Respectively, zanamivir has reduced the time to symptomatic improvement in adults, but not in children[38, 39].

Existing knowledge[16] was expanded with seven new RCTs regarding the efficacy and safety of oseltamivir and peramivir in the treatment of influenza virus infection. According to our findings, NAIs demonstrated to be effective in reducing total influenza-related complications in all patients with confirmed influenza (seasonal or pandemic). Although the effectiveness of NAIs in reducing total influenza-related complications reported a significant decrease in all patients with confirmed influenza virus infection, it ~~This finding~~ was more pronounced in high-risk patients. In literature, the mean reduction in the duration of symptoms has between 20.7-25.2 hours in the oseltamivir group[11, 14, 15] and 14 hours in the zanamivir group[38]. Among hospitalized patients, early NAI treatment has been associated with a reduction in mortality risk[11, 12]. This association, however, has been less pronounced in children[11]. Correspondingly, the risk of mortality has not decreased in patients treated with zanamivir[38].

~~Although in the analyses regarding individual respiratory influenza complications the differences were not significant, a~~ A decreasing trend favoring NAIs was observed in individual influenza complications ~~favor of NAIs versus those treated with placebo was observed~~. In line with literature[13, 14, 38], we found no difference in the risk of upper or lower respiratory tract infection following oseltamivir treatment. Conflicting results related to the risk of lower respiratory tract infection has been, however, detected. For

instance, Dobson et al[15] and Doll et al.[11] found that oseltamivir has been associated with a decrease in hospitalization and decreased risk of lower respiratory tract infections (e.g., pneumonia) and admittance to hospital. In addition, zanamivir was reduced the incidence of complications requiring antimicrobial treatment[39].

~~Several SR~~Previous literature, including both RCT and observational studies, have focused on the effectiveness and safety of NAIs ~~administration~~ in reducing the severity (e.g., hospitalization), transmission, and the length of influenza illness in healthy adults exposed to naturally occurring influenza[9,11,12, 13]. ~~, but there is S~~scarce evidence verifying their impact on preventing and treating of serious complications (such as pneumonia, bronchiolitis, sinusitis, otitis media), however, has been observed[13–15,38,39] whereas a lack of good data has undermined previous findings regarding oseltamivir[13].

No significant difference was reported in the occurrence of total drug-related AEs between patients treated with NAIs vs. placebo. NAIs are safe to use in all patients with confirmed influenza to reduce gastrointestinal problems such as diarrhea by viral origin, although they could cause nausea or vomit group[41,42]; in literature, oseltamivir has induced the risk of nausea and vomiting for 1.5- to 2.5-fold[11, 13, 15]. In line with Boikos et al.[9], however, data for children and pregnant women are limited.

Limitations should be considered when interpreting the results of this systematic review. The main limitation is the heterogeneity regarding the study populations and the administered antiviral agents, as well as the scarce data regarding the incidence of individual influenza complications (more RCTs are needed), so that explains for the non-significant differences observed in the respective comparisons. Although the majority of the included trials were reported to have a double-blind design, detailed information regarding the type of randomization or the allocation concealment was scarce, and, one small open-label study was included.

Despite these limitations, our study provides information about a gap in the published literature, being an important strength and having implications for further research. Furthermore, the results were based on RCTs, rather than observational cohort studies so that it illustrates the need for research in form of RCTs in the subset of patients with seasonal and pandemic influenza, focusing on meaningful pre-defined outcome criteria. Future research should focus on…

Conclusion

NAIs comparing placebo therapy did demonstrate to be effective and safe in reducing total influenza-related complications in both low- and high-risk patients. However, the effectiveness of NAIs in separate data of influenza-related complications did demonstrate a trend benefit in favor of NAIs versus those treated with placebo.

Conflict of interest

JR served as a consultant and received grant support from Genentech and ROCHE. Other authors have not disclosed any conflict of interest.

Funding

This work was funded by CIBERES, Instituto Salud Carlos III, Madrid, Spain (Fondos FEDER) (CB06-06-036).

Acknowledgments

This study was part of the doctoral thesis from STM at Medicine Department, University of Barcelona.

References

1. Rath B, Conrad T, Myles P, et al. Influenza and other respiratory viruses: standardizing disease severity in surveillance and clinical trials. *Expert Rev Anti Infect Ther*. 2017;15(6):545-568. doi:10.1080/14787210.2017.1295847

2. Rello J, Rodríguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care*. 2009;13(5):R148. doi:10.1186/cc8044

3. Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet*. 2018;391(10127):1285-1300. doi:10.1016/S0140-6736(17)33293-2

4. Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec*. 2012;87(47):461-476.

5. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018-19 Influenza Season. *MMWR Recomm Rep*. 2018;67(3):1-20. doi:10.15585/mmwr.rr6703a1

6. Gubareva LV, Besselaar TG, Daniels RS, et al. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2015-2016. *Antiviral Res*. 2017;146:12-20. doi:10.1016/j.antiviral.2017.08.004

7. European Centre for Disease Prevention and Control (ECDC). Public health use of influenza antivirals during influenza pandemics. ECDC Interim guidance 2009.

8. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. *Clin Infect Dis*. 2019;68(6):895-902. doi:10.1093/cid/ciy874

9. Boikos C, Caya C, Doll MK, et al. Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009-15. *J Antimicrob Chemother*. 2017;72(6):1556-1573. doi:10.1093/jac/dkx013

10. Tejada S, Campogiani L, Solé-Lleonart C, Rello J. Alternative Regimens of Neuraminidase Inhibitors for Therapy of Hospitalized Adults with Influenza: A Systematic Review of Randomized Controlled Trials. *Adv Ther*. 2020. doi:10.1007/s12325-020-01347-5

11. Doll MK, Winters N, Boikos C, Kraicer-Melamed H, Gore G, Quach C. Safety and effectiveness of neuraminidase inhibitors for influenza treatment, prophylaxis, and outbreak control: a systematic review of systematic reviews and/or meta-analyses. *J Antimicrob Chemother*. 2017;72(11):2990-3007. doi:10.1093/jac/dkx271

12. 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. doi:10.1016/S2213-2600(14)70041-4

13. Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ*. 2009;339:b5106. doi:10.1136/bmj.b5106

14. Ebell MH, Call M, Shinholser J. Effectiveness of oseltamivir in adults: a meta-analysis of published and unpublished clinical trials. *Fam Pract*. 2013;30(2):125-133. doi:10.1093/fampra/cms059

15. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*. 2015;385(9979):1729-1737. doi:10.1016/S0140-6736(14)62449-1

16. Falagas ME, Koletsi PK, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Rello J. Effectiveness and safety of neuraminidase inhibitors in reducing influenza complications: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2010;65(7):1330-1346. doi:10.1093/jac/dkq158

17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34. doi:10.1016/j.jclinepi.2009.06.006

18. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 [updated March 2011]. http://www.cochrane-handbook.org. Accessed June 21, 2019.

19. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13. doi:10.1186/1471-2288-5-13

20. Beigel JH, Manosuthi W, Beeler J, et al. Effect of Oral Oseltamivir on Virological Outcomes in Low-risk Adults With Influenza: A Randomized Clinical Trial. *Clin Infect Dis*. 2019. doi:10.1093/cid/ciz634

21. Dawood FS, Jara J, Gonzalez R, et al. A randomized, double-blind, placebo-controlled trial evaluating the safety of early oseltamivir treatment among children 0-9 years of age hospitalized with influenza in El Salvador and Panama. *Antiviral Res*. 2016;133:85-94. doi:10.1016/j.antiviral.2016.07.007

22. 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. doi:10.1016/S1473-3099(13)70267-6

23. 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 Off Publ Infect Dis Soc Am*. 2010;51(8):887-894. doi:10.1086/656408

24. Lin J-T, Yu X-Z, Cui D-J, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. *Curr Med Res Opin*. 2006;22(1):75-82. doi:10.1185/030079906X80297

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. doi:10.1097/01.inf.0000154322.38267.ce

26. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20(2):127-133. doi:10.1097/00006454-200102000-00002

27. Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet*. 2000;355(9218):1845-1850. doi:10.1016/s0140-6736(00)02288-1

28. 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. doi:10.1001/jama.283.8.1016

29. Puhakka T, Lehti H, Vainionpää R, et al. Zanamivir: a significant reduction in viral load during treatment in military conscripts with influenza. *Scand J Infect Dis*. 2003;35(1):52-58. doi:10.1080/0036554021000026981

30. Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *Pediatr Infect Dis J*. 2000;19(5):410-417. doi:10.1097/00006454-200005000-00005

31. Murphy KR, Eivindson A, Pauksens K, et al. Efficacy and Safety of Inhaled Zanamivir for the Treatment of Influenza in Patients with Asthma or Chronic Obstructive Pulmonary Disease. *Clin Drug Investig*. 2000;20(5):337-349. doi:10.2165/00044011-200020050-00005

32. Mäkelä MJ, Pauksens K, Rostila T, et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. *J Infect*. 2000;40(1):42-48. doi:10.1053/jinf.1999.0602

33. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet*. 1998;352(9144):1877-1881.

34. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. *N Engl J Med*. 1997;337(13):874-880. doi:10.1056/NEJM199709253371302

35. de Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. *Clin Infect Dis*. 2014;59(12):e172-185. doi:10.1093/cid/ciu632

36. Whitley R, Laughlin A, Carson S, et al. Single dose peramivir for the treatment of acute seasonal influenza: integrated analysis of efficacy and safety from two placebo-controlled trials. *Antivir Ther (Lond)*. 2015;20(7):709-719. doi:10.3851/IMP2874

37. Kohno S, Kida H, Mizuguchi M, Shimada J, S-021812 Clinical Study Group. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2010;54(11):4568-4574. doi:10.1128/AAC.00474-10

38. Heneghan CJ, Onakpoya I, Thompson M, Spencer EA, Jones M, Jefferson T. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2547. doi:10.1136/bmj.g2547

Formatted: Finnish

39. Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Arch Intern Med*. 2001;161(2):212-217. doi:10.1001/archinte.161.2.212

40. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2014;(4):CD008965. doi:10.1002/14651858.CD008965.pub4

41. Hata A, Akashi-Ueda R, Takamatsu K, Matsumura T. Safety and efficacy of peramivir for influenza treatment. *Drug Des Devel Ther*. 2014;8:2017-2038. doi:10.2147/DDDT.S46654

42. Lee J, Park JH, Jwa H, Kim YH. Comparison of Efficacy of Intravenous Peramivir and Oral Oseltamivir for the Treatment of Influenza: Systematic Review and Meta-Analysis. *Yonsei Med J*. 2017;58(4):778-785. doi:10.3349/ymj.2017.58.4.778

Table 1. Main characteristics of the randomized controlled trials (RCTs) included in the meta-analysis.

Study	Country	Study period	Study design	Intervention	Control	Concomitant treatment	Intention to treat population (ITT)	Laboratory-confirmed influenza (IPP)	Follow-up
Oseltamivir trials									
Beigel et al., 2019	Thailand, USA, Argentina	01/2012 – 10/2017	Double-blind, multicentre	Oseltamivir oral 75 mg twice daily for 5 days	Placebo twice daily for 5 days	Any prescription medications or over-the-counter preparations	558	501	28 days
Dawood et al., 2016	El Salvador, Panama	09/2012 – 10/2012 and 04/2013 – 10/2013	Phase IV, Double-blind, multicentre	£ Oseltamivir oral 75 mg twice daily for 5 days	Placebo twice daily for 5 days	Antibiotic	688	683	7 days after discharge
Fry et al., 2014	Bangladesh	05/2008 – 12/2010	Phase III, Double-blind, multicentre	Oseltamivir 75 mg twice daily for 5 days	Placebo twice daily for 5 days	Antibiotics, paracetamol	1190	1163	2, 4, and 7 days
Heinonen et al., 2010	Finland	2007–2008 and 2008–2009	Phase IV, double-blind, single-centre	¥ Oseltamivir oral 30 mg or 45 mg twice daily for 5 days	Placebo twice daily for 5 days	antipyretics and/or analgesics	408	98	5-8 days
Lin et al., 2006	China	2002–2003	Open-label, multicentre	Oseltamivir oral 75 mg twice daily for 5 days	Symptomatic treatment for 5 days	Acetaminophen + antibiotics	118	56	21 days
Johnston et al., 2005	NR	1998–1999	Double-blind, multicentre	Oseltamivir oral 2 mg/kg twice daily for 5 days	Placebo twice daily for 5 days	paracetamol, acetaminophen, antihistamines, corticosteroids	334	179	6 days, 10 days, 28 days
Whitley et al., 2001	USA, Canada	1998–1999	Double-blind, multicentre	Oseltamivir oral 2 mg/kg twice daily for 5 days	Placebo twice daily for 5 days	acetaminophen	695	452	28 days
Nicholson et al., 2000	Europe, Canada, China	01/1998 – 03/1998	Double-blind, multicentre	Oseltamivir oral 75 or 150 mg twice daily for 5 days	Placebo twice daily for 5 days	paracetamol	726	475	21 days
Treanor et al., 2000	USA	01/1998 – 03/1998	Double-blind, multicentre	Oseltamivir oral 75 or 150 mg twice daily for 5 days	Matching Placebo for 5 days	acetaminophen	629	NR	21 days
Zanamivir trials									
Puhakka et al., 2003	Finnish Defence Forces	2000–2001	Double-blind, multicentre	Zanamivir inhaled 10 mg twice daily for 5 days	Placebo twice daily for 5 days	paracetamol	588	435	28 days
Hedrick et al., 2000	USA, Canada, Europe/Israel	1998 – 1999	Double-blind, multicentre	Zanamivir inhaled 10 mg twice daily for 5 days	Placebo for 5 days	acetaminophen, paracetamol, dextromethorphan/pholcodine	471	346	28 days
Murphy et al., 2000	USA, Canada, Europe, Chile, Australia, South Africa	04/1998 – 02/2000	Double-blind, multicentre	Zanamivir inhaled 10 mg twice daily for 5 days	Placebo twice daily for 5 days	acetaminophen, paracetamol, dextromethorphan/pholcodine	525	313	28 days
Mäkelä et al., 2000	Europe	1997–1998	Phase III, Double-blind, multicentre	Zanamivir inhaled 10 mg twice daily for 5 days	Matching Placebo for 5 days	paracetamol, dextromethorphan	356	277	14 days, 28 days
The MIST study group, 1998	Australia, New Zealand, South Africa	1997	Phase III, Double-blind, multicentre	Zanamivir inhaled 10 mg twice daily for 5 days	Placebo twice daily for 5 days	paracetamol, pholcodine cough mixture	455	321	28 days
Hayden et al., 1997	USA, Europe	1994–1995	Double-blind, multicentre	A. Zanamivir inhaled 10 mg + zanamivir intranasal spray 6.4 mg twice daily for 5 days B. Zanamivir inhaled 10 mg + placebo nasal spray twice daily for 5 days	Placebo both routes twice daily for 5 days	acetaminophen, dextromethorphan, hydrobromide, pseudoepinephrine	417	262	NR

Peramivir trials									
De Jong et al., 2014	Argentina, Europe, Brazil, Canada, Chile, India, Israel, Lebanon, Peru, Russia, Serbia, South Africa, Ukraine, USA	09/2009 – 11/2012	Phase III, double-blind, multicentre	Peramivir intravenous 600 mg once daily for 5 days	Placebo once daily for 5 days	SOC: Oseltamivir was administered during the study to 5 subjects (12%) in the placebo group and 3 (4%) in the peramivir group.	*121	NR	NR
Whitley et al., 2015	211 study Canada, USA	01/2007 – 09/2007	Phase II, double-blind, multicentre	Peramivir Intravenous 150 or 300 mg once daily	Placebo both routes for 5 days	NR	344	319	NR
	311 study USA	01/2008 – 02/2008	Phase III, double-blind, multicentre	Peramivir Intravenous 300 mg once daily	Placebo 300 mg once daily		83	82	
Kohno et al., 2010	Japan	12/2007 – 04/2008	Double-blind, multicentre	Peramivir Intravenous 300 or 600 mg once daily	Placebo once daily	Acetaminophen	298	296	14 days

NR: Not Reported; RT-PCR: Real Time Polymerase Chain Reaction; COPD: Chronic Obstructive Pulmonary Disease; RAT: Rapid Antigen Test

£ For children aged 0-11 months, study drug was dosed at 3 mg/kg/dose. For children aged >12 months, study drug was dosed based on standard unit dosing: 30 mg/dose for children ≤15 kg, 45 mg for children >15-23 kg, 60 mg for children >23-40 kg, and 75 mg for children >40 kg. ¥ For children weighing ≤15.0 kg, study drug was dosed at 30 mg. For children weighing 15.1–23.0 kg, study drug was dosed at 45 mg. *Only ITTI non-NAI SOC group included. The ITTI NAI SOC group was excluded due to administration of rimantadine and amantadine.

Table 2. Baseline characteristics of the study population of the included in the meta-analysis

Study	Inclusion criteria	Diagnosis	Hours from onset of illness to enrolment, mean (SD)	Influenza type % (n)	Complications % (n)	Vaccination % (n)	Antibiotics % (n)
Oseltamivir trials							
Beigel et al., 2019	Adults 18-64 years old. One or more respiratory symptoms (cough, sore throat, or nasal symptoms), onset of respiratory symptoms no more than 48 h before enrollment	RAT, PCR	30 (3.0) vs 27.7 (2.8)	A/H1N1: 10.4 (58/556) A/H3N2: 16.3 (91/556) B: 28.1 (156/556)	Sinusitis: 1.3 (7/501) Otitis media: 0.2 (1/501) Bronchitis: 1.2 (6/501) Pneumonia: 0.2 (1/501)	10.2 (57/556)	2.2 (11/501)
Dawood et al., 2016	Children ≤ 9 years old. Hospitalized <7 days after symptom onset with symptoms meeting a modified version of the World Health Organization criteria for severe acute respiratory infection (cough or sore throat plus age-specific tachypnea)	RT-PCR	76.5 (7.6) vs 62.2 (9.8)	A/H1N1: 0.7 (5/683) A/H3N2: 3.1 (21/683) B: 0.3 (2/683)	Asthma: 16.6 (5/30)	NR	60 (18/30)
Fry et al., 2014	Community residents The clinical criteria for respiratory illness included either one major sign (eg, fever, age-specific tachypnoea, breathing difficulty, noisy breathing, ear pain or discharge, or any danger sign including lethargy or changed mental status, cyanosis, convulsions, inability to drink, or chest indrawing) or two minor signs (cough, sore throat, rhinorrhea, headache, chills, myalgia, or vomiting)	RAT, PCR	48 (8.0) vs 48 (8.0)	A/H1N1: 11 (131/1190) A/H1N1pdm09: 17.8 (213/1190) A/H3N2: 35.1 (418/1190) B: 33.3 (397/1190)	NR	NR	36.4 (434/1190)
Heinonen et al., 2010	Children 1-3 years old. To be eligible, the child had for <24 h a fever (oral, rectal, or axillary temperature ≥38.0ºC) and ≥1 sign or symptom of respiratory infection (cough, rhinitis, or sore throat) or a positive RAT result	RT-PCR	11.1 (6.9) vs 8.8 (6.6)	A/H1N1: 19.3 (79/408) B: 4.6 (19/408)	Otitis media: 11.2 (11/98)	13.2 (13/98)	NR
Lin et al., 2006	Adults with chronic respiratory disease (bronchial asthma, bronchiectasis, obstructive pulmonary emphysema) or chronic cardiac disease (coronary heart disease or chronic heart insufficiency) with symptoms consistent with influenza infection (fever ≥37.8ºC and ≥2 following symptoms: sore throat, cough, nasal snuffle, myalgia, fatigue, headache, chills/sweating) and presented within 48 h of illness onset	viral culture, serology	NR	NR	Bronchial asthma: 21.4 (12/56)	NR	NR
Johnston et al., 2005	Children 6–12 years old. Severe asthma requiring regular medical follow-up monitoring or hospital care that presented with influenza symptoms [recorded temperature of ≥100ºF (≥38.7ºC) plus 1 respiratory symptom (cough or coryza)], presented within 48 h after symptom onset and were able to perform the pulmonary function tests	viral culture, serology	27.9 (11.6) vs 26.8 (11.5)	NR	NR	19.3 (25/179)	NR
Whitley et al., 2001	Children 1–2 years old. Presenting within 48h of illness onset and having an oral/otic temperature ≥37.8ºC and ≥1 respiratory symptom (cough or coryza)	viral culture, serology	26.7 (NR) vs 28.0 (NR)	A/H1N1: 67 (303/452) B: 32.7 (148/452)	Otitis media: 15.2 (69/452)	2.2 (10/452)	NR
Nicholson et al., 2000	Adults 18–65 years old. Presented within 36 h of onset of influenza-like illness with fever ≥38ºC with at least 1 respiratory symptom (cough, sore throat or nasal symptom) and at least 1 constitutional symptom (headache, malaise, myalgia, sweats or chills, or fatigue)	viral culture, serology	14 (2.6) vs 12.7 (3.1) vs 14 (2.6)	A/H1N1: 96.6 (459/475) B: 3.3 (16/475)	NR	Excluded	NR
Treanor et al., 2000	Adults 18–65 years old. Previously healthy presented within 36 h of onset of influenza symptoms and had documented oral temperature of ≥38ºC at enrolment plus ≥1 respiratory symptom (cough, sore throat or nasal symptoms) and ≥1 constitutional symptom (headache, malaise, myalgia, sweats and/or chills or fatigue); women were required to have a negative urine pregnancy test before drug administration	viral culture, serology	22.2 (6.8) vs 23.2 (5.8) vs 23.2 (6.1)	A/H1N1: 54.7 (343/627) B: 1.4 (9/627)	NR	Excluded	NR
Zanamivir trials							
Puhakka et al., 2003	all conscripts of the Finnish Defence Forces of 6 garrisons who had influenza-like illness (defined as fever temperature ≥37.8ºC of <48 h duration and ≥2 of the following: headache, muscle/joint aches and pain, sore throat and cough)	viral culture, PCR, serology	23.6 (11.4) vs 24.5 (11.4)	A/H1N1: 73.2 (431/588) B: 0.6 (4/588)	NR	0.5 (3/588)	Excluded
Hedrick et al., 2000	Children 5–12 years old. Influenza-like illness of ≤36 h defined by the presence of fever (≥37.8ºC) and no clinical evidence of bacterial infection	viral culture, PCR, serology	21.6 (9.3) vs 20.1 (9.0)	A/H1N1: 49.9 (226/471) B: 25.4 (120/471)	NR	0.6 (3/471)	NR

Murphy et al., 2000	Patients ≥12 years old. Asthma or COPD with an acute influenza-like illness of <36 h defined as the presence of fever (temperature ≥37.8ºC) and ≥2 of the following symptoms: sore throat, cough, headache, muscle or joint aches and pains	viral culture, PCR, serology	22.5 (7.8) vs 22.7 (8.1)	A/H1N1: 54.1 (284/525) B: 5.3 (28/525)	Asthma: 76 (399/525)	23.2 (122/525)	NR
Mäkelä et al., 2000	Patients ≥12 years old. Recruited within 2 days of onset of typical influenza symptoms (≥37.8ºC for patients ,65 years, ≥37.2ºC for patients ≥65 years) and ≥2 of the following symptoms: headache, myalgia, cough and sore throat	Viral culture, PCR, ELISA	NR	A/H3N2: 96 (265/277) B: 4 (12/598)	NR	Total 4 (14/277)	NR
The MIST study group, 1998	Patients ≥ 12 years old. Previously health who presented with influenza-like illness (fever ≥37.8ºC), feverishness, or both, and at least 2 of myalgia, cough, headache or sore throat of ≤36 h	serology	24.8 (7.4) vs 25.0 (7.4)	A/H1N1: 47 (214/455) B: 14.7 (67/455)	NR	5.7 (26/455)	NR
Hayden et al., 1997	Adults ≥ 18 years old (≥13 years in North America). Previously healthy with an acute influenza-like illness of ≤48 h duration; illness was defined as the presence of fever and at least 2 other symptoms (headache, myalgia, cough and sore throat)	viral culture, serology	59 (17) vs 58 (17)	A/H1N1: 55.7 (97/174) B: 44.2 (77/174)	NR	Excluded	NR
Peramivir trials							
De Jong et al., 2014	Adults (≥ 18 years), adolescents (11-12 years), or children 6-11 years old. Fever and/or reduced oxygen saturation (Tª ≥38.0°C (≥100.4°F) oral, or ≥38.6°C (≥101.4°F) tympanic or rectal; oxygen saturation <92%), ≥2 of 3 vital signs abnormal (Respiration rate as >30/min in children; >24/min in adults; Heart rate as >110/min in children; >100/min in adults; Systolic blood pressure as <80 mm Hg in children; <90 mm Hg in adults), ≥1 respiratory symptom for <72 h (Cough, sore throat, or nasal congestion), ≥1 constitutional symptom for <72 h (Headache, myalgia, feverishness, or fatigue), or ≥1 risk factor (Illness severity that in the investigator's opinion justified hospitalization; age ≥60 y; presence of COPD or other chronic lung disease requiring daily pharmacotherapy; current history of congestive heart failure or angina; diabetes mellitus, clinically stable or unstable; transcutaneous oxygen saturation <94% (without supplemental oxygen for ≥5 min), or a medically significant decrease in oxygen saturation from an established baseline; history of chronic renal impairment not requiring peritoneal dialysis; serum creatinine >2.0mg/dL or >177 µmol/L)	RAT, RT-PCR	NR	A/H1N1pdm09: 20.6 (25/121) A/H3N2: 50.4 (61/121) B: 23.9 (29/121)	NR	4.9 (6/121)	NR
Whitley et al., 2015	Adults ≥ 18 years old. Previously healthy males and non-pregnant females who presented within 48h of onset of influenza symptoms with positive RAT for influenza A or B performed at clinic site and who had documented fever ≥38ºC (oral), ≥ 1 respiratory symptoms (cough, sore throat or nasal symptoms) and one or more constitutional symptoms (headache, myalgia, feverishness or fatigue)	RAT, RT-PCR	NR	A/H1N1: 24.3 (104/427) A/H3N2: 48.7 (208/427) B: 18.2 (78/427)	NR	Excluded (immunization within 21 days)	NR
Kohno et al., 2010	Adults 20-64 years old. Previously healthy adults reporting onset of influenza-like illness within the previous 48 h. The time of onset of influenza-like illness was defined as either when the body temperature first rose to >1°C above normal or when the subject experienced at least two of the seven influenza symptoms (headache, aches or pains in muscles or joints, feverishness, fatigue, cough, sore throat, and nasal congestion). At enrollment, a diagnosis of influenza was required based on a positive RAT for influenza virus, fever of ≥38°C, and the presence of at least two of the seven symptoms listed above at moderate to high severity	Viral culture, PCR, serology	57.2 (NR) vs 56.1 (NR) vs 86.7 (NR)	A/H1N1: 72.6 (215/296) A/H3N2: 23.6 (70/296) B: 1 (3/296)	NR	Excluded (immunization within 7 days)	NR

COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NT: not reported; RAT: rapid antigen test; SD: standard deviation

Table 3. Other efficacy outcomes

Outcomes	Odd Ratio	95% CI	p-value	I^2
Pneumonia	0.44	0.10 – 2.00	0.29	49%
Acute otitis media	0.50	0.31 – 0.82	<0.01	0%
Asthma exacerbations	0.57	0.28 – 1.16	0.12	0%
Hospitalizations	0.57	0.24 – 1.38	0.21	0%
Antibiotic treatment	0.64	0.46 – 0.90	<0.01	46%
Sinusitis	0.73	0.40 – 1.32	0.30	0%
Bronchitis	0.80	0.43 – 1.48	0.47	5%
Study withdrawal due to adverse events	1.11	0.69 – 1.79	0.66	0%

FIGURE LEGENDS

Figure 1. A) "Risk of bias" graph: authors' judgments about each risk of bias item presented as percentages across all included studies. B) "Risk of bias" summary: authors' judgments about each risk of bias item presented as percentages for each of the included study

Figure 2. Forest plot of time to clinical resolution of patients with laboratory-confirmed influenza, that were treated with oseltamivir, zanamivir, or peramivir compared with placebo

Figure 3. Forest plot of total influenza-related complications: (A) laboratory-confirmed influenza patients treated with oseltamivir, zanamivir, or peramivir compared with placebo. (B) laboratory-confirmed influenza patients, as well as high-risk patients, that were treated with NAIs compared with placebo. (C) Pediatric and adult patients with laboratory-confirmed influenza

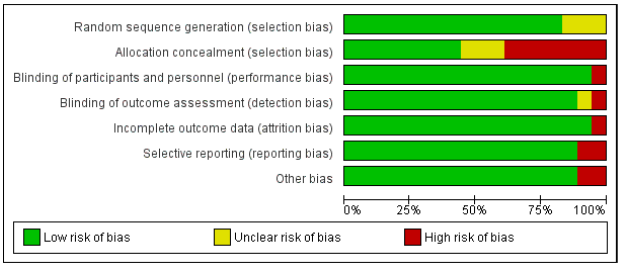
Figure 4. Forest plot of total related-drug AEs, nausea/vomiting, and diarrhea occurring in patients treated with NAIs compared with placebo

Additional file 2. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the study selection

Additional file 4. Forest plot of (A) pneumonia, (B) bronchitis, (C) sinusitis, (D) asthma exacerbations, (E) acute otitis media, (F) antibiotic treatment, (G) hospitalizations, or (H) study withdrawals due to AEs of patients with laboratory-confirmed influenza, that were treated with neuraminidase inhibitors compared with placebo

Figure 1

A.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

B.

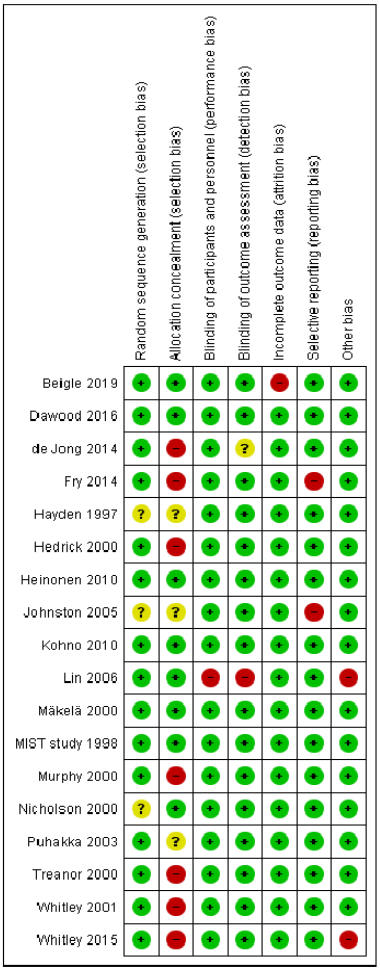

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Beigle 2019
Dawood 2016
de Jong 2014
Fry 2014
Hayden 1997
Hedrick 2000
Heinonen 2010
Johnston 2005
Kohno 2010
Lin 2006
Mäkelä 2000
MIST study 1998
Murphy 2000
Nicholson 2000
Puhakka 2003
Treanor 2000
Whitley 2001
Whitley 2015

Figure 2.

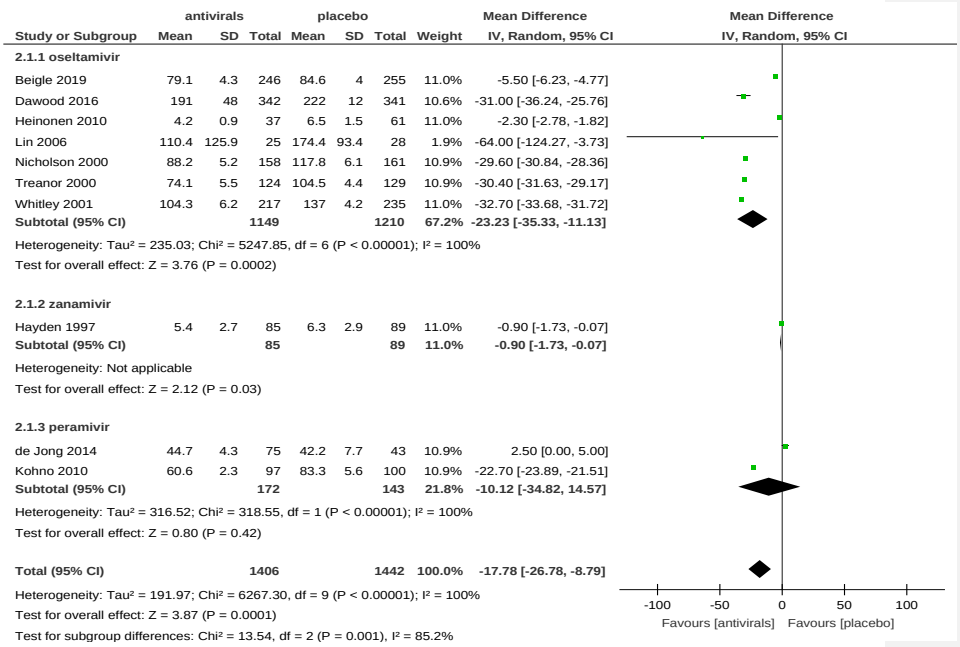
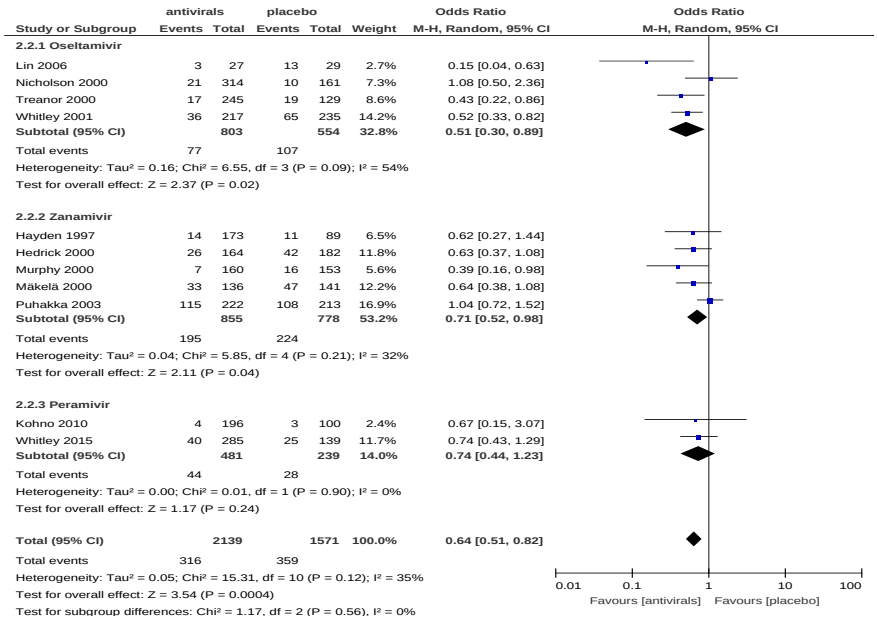
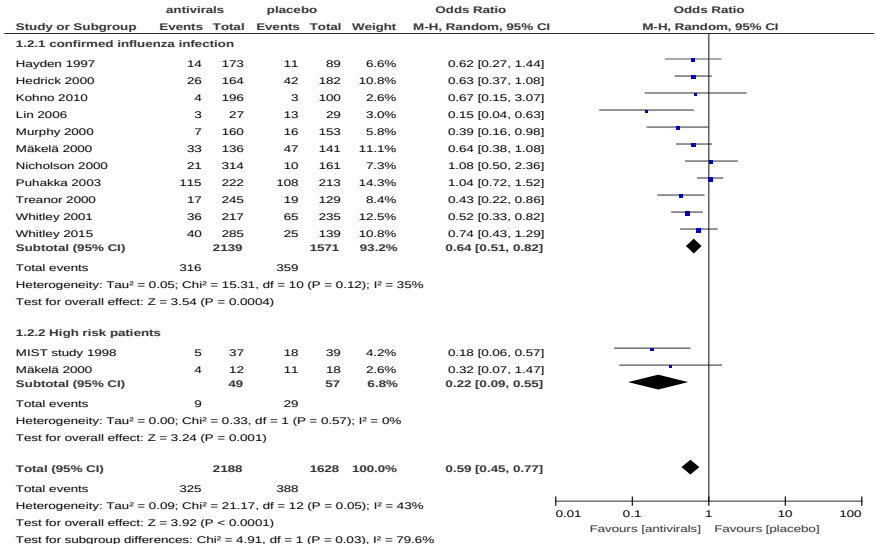

antivirals
placebo
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.1.1 oseltamivir
Beigle 2019 79.1 4.3 246 84.6 4 255 11.0% -5.50 [-6.23, -4.77]
Dawood 2016 191 48 342 222 12 341 10.6% -31.00 [-36.24, -25.76]
Heinonen 2010 4.2 0.9 37 6.5 1.5 61 11.0% -2.30 [-2.78, -1.82]
Lin 2006 110.4 125.9 25 174.4 93.4 28 1.9% -64.00 [-124.27, -3.73]
Nicholson 2000 88.2 5.2 158 117.8 6.1 161 10.9% -29.60 [-30.84, -28.36]
Treanor 2000 74.1 5.5 124 104.5 4.4 129 10.9% -30.40 [-31.63, -29.17]
Whitley 2001 104.3 6.2 217 137 4.2 235 11.0% -32.70 [-33.68, -31.72]
Subtotal (95% CI) 1149 1210 67.2% -23.23 [-35.33, -11.13]
Heterogeneity: Tau² = 235.03; Chi² = 5247.85, df = 6 (P < 0.00001); I² = 100%
Test for overall effect: Z = 3.76 (P = 0.0002)
2.1.2 zanamivir
Hayden 1997 5.4 2.7 85 6.3 2.9 89 11.0% -0.90 [-1.73, -0.07]
Subtotal (95% CI) 85 89 11.0% -0.90 [-1.73, -0.07]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)
2.1.3 peramivir
de Jong 2014 44.7 4.3 75 42.2 7.7 43 10.9% 2.50 [0.00, 5.00]
Kohno 2010 60.6 2.3 97 83.3 5.6 100 10.9% -22.70 [-23.89, -21.51]
Subtotal (95% CI) 172 143 21.8% -10.12 [-34.82, 14.57]
Heterogeneity: Tau² = 316.52; Chi² = 318.55, df = 1 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.80 (P = 0.42)
Total (95% CI) 1406 1442 100.0% -17.78 [-26.78, -8.79]
Heterogeneity: Tau² = 191.97; Chi² = 6267.30, df = 9 (P < 0.00001); I² = 100%
Test for overall effect: Z = 3.87 (P = 0.0001)
Test for subgroup differences: Chi² = 13.54, df = 2 (P = 0.001), I² = 85.2%
-100
-50
0
50
100
Favours [antivirals]
Favours [placebo]

Figure 3.

A.


antivirals
placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.2.1 Oseltamivir
Lin 2006 3 27 13 29 2.7% 0.15 [0.04, 0.63]
Nicholson 2000 21 314 10 161 7.3% 1.08 [0.50, 2.36]
Treanor 2000 17 245 19 129 8.6% 0.43 [0.22, 0.86]
Whitley 2001 36 217 65 235 14.2% 0.52 [0.33, 0.82]
Subtotal (95% CI) 803 554 32.8% 0.51 [0.30, 0.89]
Total events 77 107
Heterogeneity: Tau² = 0.16; Chi² = 6.55, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 2.37 (P = 0.02)
2.2.2 Zanamivir
Hayden 1997 14 173 11 89 6.5% 0.62 [0.27, 1.44]
Hedrick 2000 26 164 42 182 11.8% 0.63 [0.37, 1.08]
Murphy 2000 7 160 16 153 5.6% 0.39 [0.16, 0.98]
Mäkelä 2000 33 136 47 141 12.2% 0.64 [0.38, 1.08]
Puhakka 2003 115 222 108 213 16.9% 1.04 [0.72, 1.52]
Subtotal (95% CI) 855 778 53.2% 0.71 [0.52, 0.98]
Total events 195 224
Heterogeneity: Tau² = 0.04; Chi² = 5.85, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 2.11 (P = 0.04)
2.2.3 Peramivir
Kohno 2010 4 196 3 100 2.4% 0.67 [0.15, 3.07]
Whitley 2015 40 285 25 139 11.7% 0.74 [0.43, 1.29]
Subtotal (95% CI) 481 239 14.0% 0.74 [0.44, 1.23]
Total events 44 28
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)
Total (95% CI) 2139 1571 100.0% 0.64 [0.51, 0.82]
Total events 316 359
Heterogeneity: Tau² = 0.05; Chi² = 15.31, df = 10 (P = 0.12); I² = 35%
Test for overall effect: Z = 3.54 (P = 0.0004)
Test for subgroup differences: Chi² = 1.17, df = 2 (P = 0.56), I² = 0%
0.01 0.1 1 10 100
Favours [antivirals] Favours [placebo]

B.


antivirals
placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 confirmed influenza infection
Hayden 1997 14 173 11 89 6.6% 0.62 [0.27, 1.44]
Hedrick 2000 26 164 42 182 10.8% 0.63 [0.37, 1.08]
Kohno 2010 4 196 3 100 2.6% 0.67 [0.15, 3.07]
Lin 2006 3 27 13 29 3.0% 0.15 [0.04, 0.63]
Murphy 2000 7 160 16 153 5.8% 0.39 [0.16, 0.98]
Mäkelä 2000 33 136 47 141 11.1% 0.64 [0.38, 1.08]
Nicholson 2000 21 314 10 161 7.3% 1.08 [0.50, 2.36]
Puhakka 2003 115 222 108 213 14.3% 1.04 [0.72, 1.52]
Treanor 2000 17 245 19 129 8.4% 0.43 [0.22, 0.86]
Whitley 2001 36 217 65 235 12.5% 0.52 [0.33, 0.82]
Whitley 2015 40 285 25 139 10.8% 0.74 [0.43, 1.29]
Subtotal (95% CI) 2139 1571 93.2% 0.64 [0.51, 0.82]
Total events 316 359
Heterogeneity: Tau² = 0.05; Chi² = 15.31, df = 10 (P = 0.12); I² = 35%
Test for overall effect: Z = 3.54 (P = 0.0004)
1.2.2 High risk patients
MIST study 1998 5 37 18 39 4.2% 0.18 [0.06, 0.57]
Mäkelä 2000 4 12 11 18 2.6% 0.32 [0.07, 1.47]
Subtotal (95% CI) 49 57 6.8% 0.22 [0.09, 0.55]
Total events 9 29
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.24 (P = 0.001)
Total (95% CI) 2188 1628 100.0% 0.59 [0.45, 0.77]
Total events 325 388
Heterogeneity: Tau² = 0.09; Chi² = 21.17, df = 12 (P = 0.05); I² = 43%
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Chi² = 4.91, df = 1 (P = 0.03), I² = 79.6%
0.01 0.1 1 10 100
Favours [antivirals] Favours [placebo]

C.

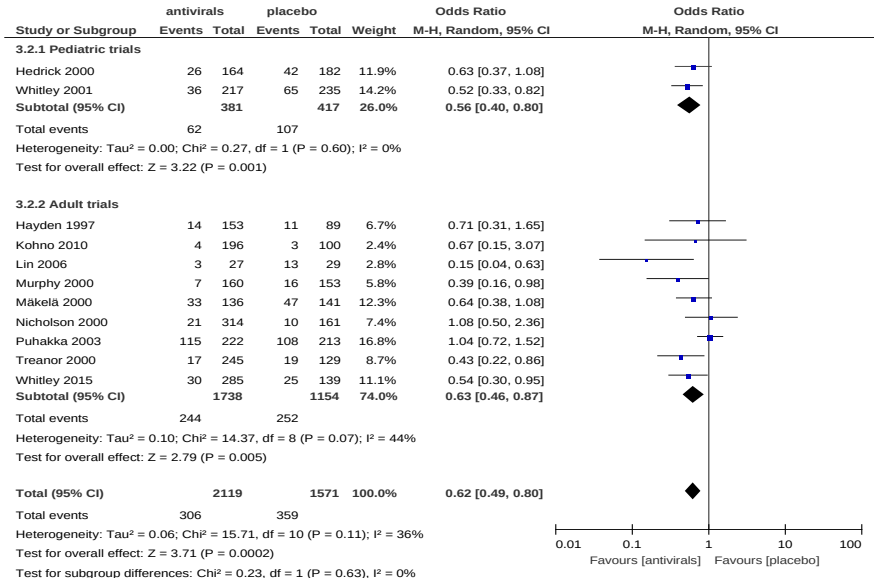
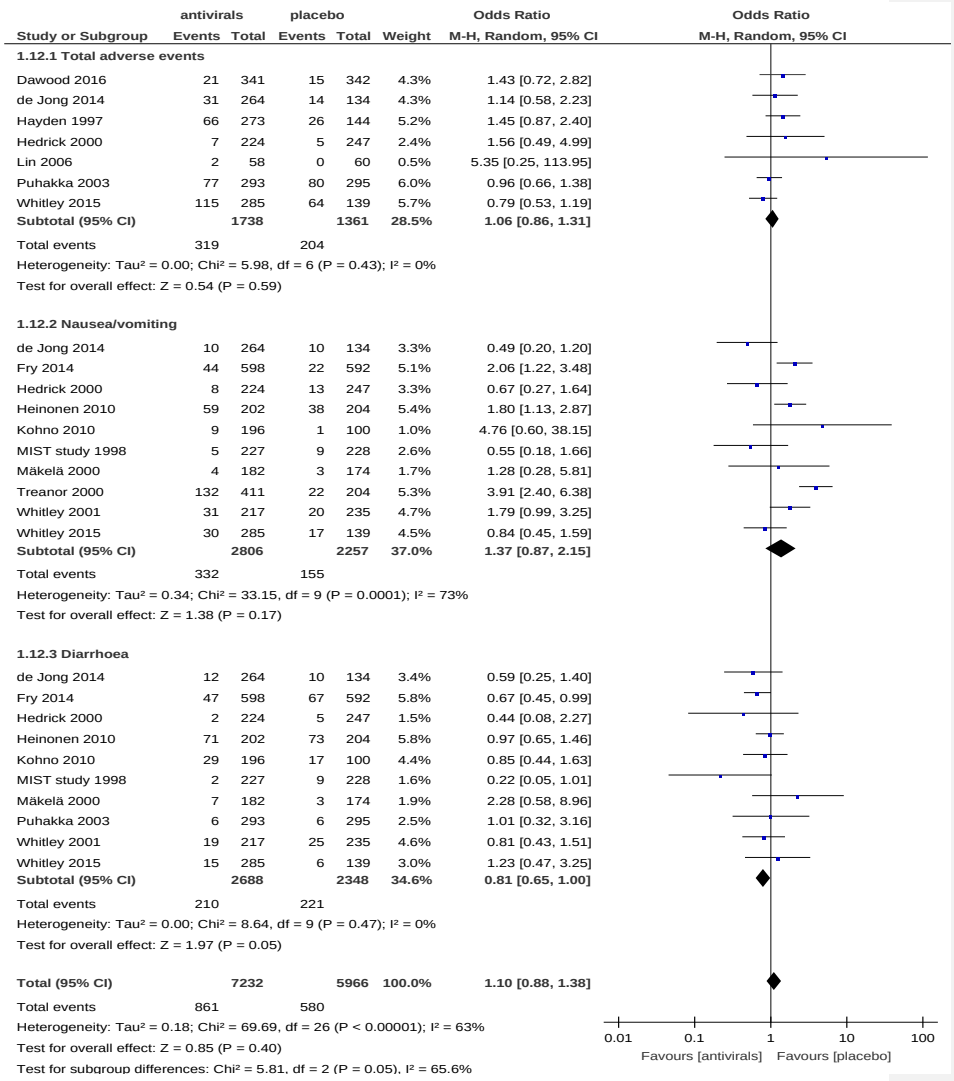

antivirals
placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
3.2.1 Pediatric trials
Hedrick 2000 26 164 42 182 11.9% 0.63 [0.37, 1.08]
Whitley 2001 36 217 65 235 14.2% 0.52 [0.33, 0.82]
Subtotal (95% CI) 381 417 26.0% 0.56 [0.40, 0.80]
Total events 62 107
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)
3.2.2 Adult trials
Hayden 1997 14 153 11 89 6.7% 0.71 [0.31, 1.65]
Kohno 2010 4 196 3 100 2.4% 0.67 [0.15, 3.07]
Lin 2006 3 27 13 29 2.8% 0.15 [0.04, 0.63]
Murphy 2000 7 160 16 153 5.8% 0.39 [0.16, 0.98]
Mäkelä 2000 33 136 47 141 12.3% 0.64 [0.38, 1.08]
Nicholson 2000 21 314 10 161 7.4% 1.08 [0.50, 2.36]
Puhakka 2003 115 222 108 213 16.8% 1.04 [0.72, 1.52]
Treanor 2000 17 245 19 129 8.7% 0.43 [0.22, 0.86]
Whitley 2015 30 285 25 139 11.1% 0.54 [0.30, 0.95]
Subtotal (95% CI) 1738 1154 74.0% 0.63 [0.46, 0.87]
Total events 244 252
Heterogeneity: Tau² = 0.10; Chi² = 14.37, df = 8 (P = 0.07); I² = 44%
Test for overall effect: Z = 2.79 (P = 0.005)
Total (95% CI) 2119 1571 100.0% 0.62 [0.49, 0.80]
Total events 306 359
Heterogeneity: Tau² = 0.06; Chi² = 15.71, df = 10 (P = 0.11); I² = 36%
Test for overall effect: Z = 3.71 (P = 0.0002)
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%
0.01
0.1
1
10
100
Favours [antivirals]
Favours [placebo]

Figure 4.

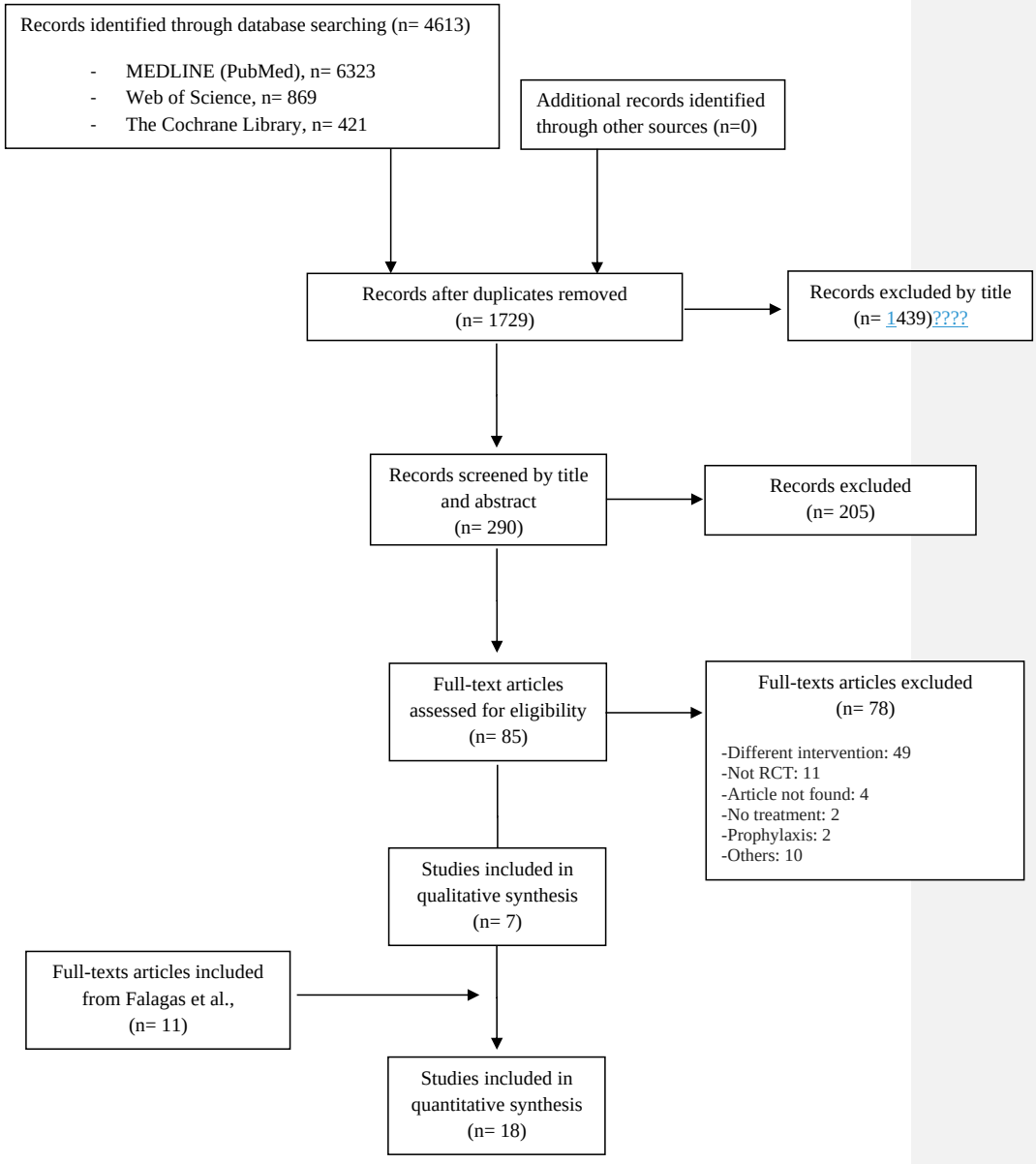

antivirals
placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.12.1 Total adverse events
Dawood 2016 21 341 15 342 4.3% 1.43 [0.72, 2.82]
de Jong 2014 31 264 14 134 4.3% 1.14 [0.58, 2.23]
Hayden 1997 66 273 26 144 5.2% 1.45 [0.87, 2.40]
Hedrick 2000 7 224 5 247 2.4% 1.56 [0.49, 4.99]
Lin 2006 2 58 0 60 0.5% 5.35 [0.25, 113.95]
Puhakka 2003 77 293 80 295 6.0% 0.96 [0.66, 1.38]
Whitley 2015 115 285 64 139 5.7% 0.79 [0.53, 1.19]
Subtotal (95% CI) 1738 1361 28.5% 1.06 [0.86, 1.31]
Total events 319 204
Heterogeneity: Tau² = 0.00; Chi² = 5.98, df = 6 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)
1.12.2 Nausea/vomiting
de Jong 2014 10 264 10 134 3.3% 0.49 [0.20, 1.20]
Fry 2014 44 598 22 592 5.1% 2.06 [1.22, 3.48]
Hedrick 2000 8 224 13 247 3.3% 0.67 [0.27, 1.64]
Heinonen 2010 59 202 38 204 5.4% 1.80 [1.13, 2.87]
Kohno 2010 9 196 1 100 1.0% 4.76 [0.60, 38.15]
MIST study 1998 5 227 9 228 2.6% 0.55 [0.18, 1.66]
Mäkelä 2000 4 182 3 174 1.7% 1.28 [0.28, 5.81]
Treanor 2000 132 411 22 204 5.3% 3.91 [2.40, 6.38]
Whitley 2001 31 217 20 235 4.7% 1.79 [0.99, 3.25]
Whitley 2015 30 285 17 139 4.5% 0.84 [0.45, 1.59]
Subtotal (95% CI) 2806 2257 37.0% 1.37 [0.87, 2.15]
Total events 332 155
Heterogeneity: Tau² = 0.34; Chi² = 33.15, df = 9 (P = 0.0001); I² = 73%
Test for overall effect: Z = 1.38 (P = 0.17)
1.12.3 Diarrhoea
de Jong 2014 12 264 10 134 3.4% 0.59 [0.25, 1.40]
Fry 2014 47 598 67 592 5.8% 0.67 [0.45, 0.99]
Hedrick 2000 2 224 5 247 1.5% 0.44 [0.08, 2.27]
Heinonen 2010 71 202 73 204 5.8% 0.97 [0.65, 1.46]
Kohno 2010 29 196 17 100 4.4% 0.85 [0.44, 1.63]
MIST study 1998 2 227 9 228 1.6% 0.22 [0.05, 1.01]
Mäkelä 2000 7 182 3 174 1.9% 2.28 [0.58, 8.96]
Puhakka 2003 6 293 6 295 2.5% 1.01 [0.32, 3.16]
Whitley 2001 19 217 25 235 4.6% 0.81 [0.43, 1.51]
Whitley 2015 15 285 6 139 3.0% 1.23 [0.47, 3.25]
Subtotal (95% CI) 2688 2348 34.6% 0.81 [0.65, 1.00]
Total events 210 221
Heterogeneity: Tau² = 0.00; Chi² = 8.64, df = 9 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Total (95% CI) 7232 5966 100.0% 1.10 [0.88, 1.38]
Total events 861 580
Heterogeneity: Tau² = 0.18; Chi² = 69.69, df = 26 (P < 0.00001); I² = 63%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Chi² = 5.81, df = 2 (P = 0.05), I² = 65.6%
0.01
0.1
1
10
100
Favours [antivirals]
Favours [placebo]

Additional file 1. List of Terms of the Search Strategy

#1	"Pneumonia" [Mesh]
#2	"Respiration disorders" [Mesh]
#3	"Respiratory tract Infections" [Mesh]
#4	Pneumonia [tiab]
#5	Viral infection [tiab]
#6	Respiratory infection [tiab]
#7	Influenza [tiab]
#8	Flu [tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	"Influenza, human" [Mesh]
#11	"Orthomyxoviridae" [Mesh]
#12	Influenza A [tiab]
#13	Influenza B [tiab]
#14	H1N1 [tiab]
#15	H3N2 [tiab]
#16	#10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	"Antiviral Agents" [Mesh]
#18	Antiviral [tiab]
#19	Anti-infectious [tiab]
#20	"Oseltamivir" [Mesh]
#21	"Zanamivir" [Mesh]
#22	Oseltamivir [tiab]
#23	Zanamivir [tiab]
#24	Peramivir [tiab]
#25	Laninamivir [tiab]
#26	Neuraminidase inhibitor* [tiab]
#27	NAI [tiab]
#28	NA inhibitor* [tiab]
#29	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30	#9 AND #16 AND #29

Additional file 2.

Commented [MJ4]: What happened to 1000 studies after duplicate removal: 1729 → 290?



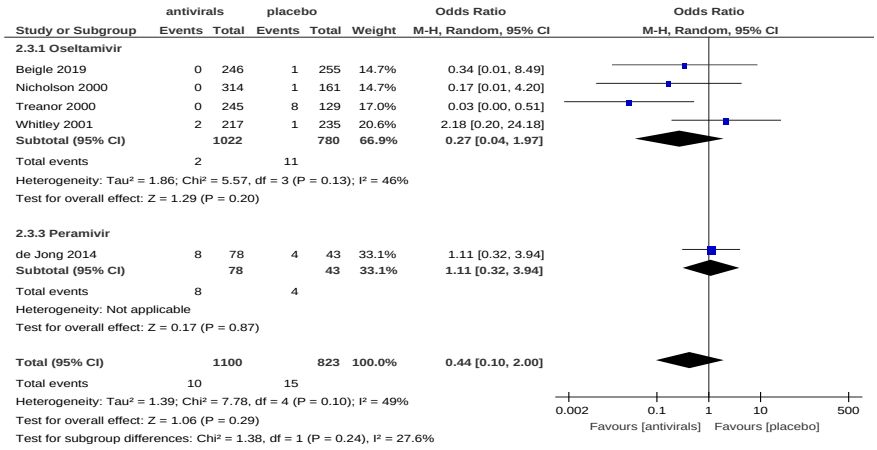
Additional file 3.

Study	Illness duration	Total influenza related complications	Pneumonia	bronchitis	Asthma exacerbations	sinusitis	Pharyngitis/ tonsillitis	Acute otitis media	Additional antibiotic treatment	hospitalizations	mortality	Drug-related AEs	Study withdrawals due to AEs
Oseltamivir trials													
Beigel et al. 2019	★		★	★		★		★	★				
Dawood et al. 2016	★								★				
Fry et al. 2014										★		★	
Heinonen et al. 2010	★							★					★
Lin et al. 2006	★	★							★	★		★	
Johnston et al. 2005					★					★			★
Whitley et al. 2001	★	★	★					★	★	★			★
Nicholson et al. 2000	★	★	★	★		★		★	★				
Treanor et al. 2000	★	★	★	★		★		★	★				★
Zanamivir trials													
Puhakka et al. 2003		★							★			★	★
Hedrick et al. 2000		★			★				★			★	
Murphy et al. 2000		★								★			★
Mäkelä et al. 2000		★×											★
The MIST study et al. 1998		×							×				★
Hayden et al. 1997	★	★							★			★	★
Peramivir trials													
De Jong et al. 2014	★		★	★		★					★	★	★
Whitley et al. 2015		★			★		★					★	★
Kohno et al. 2010	★	★		★				★					★

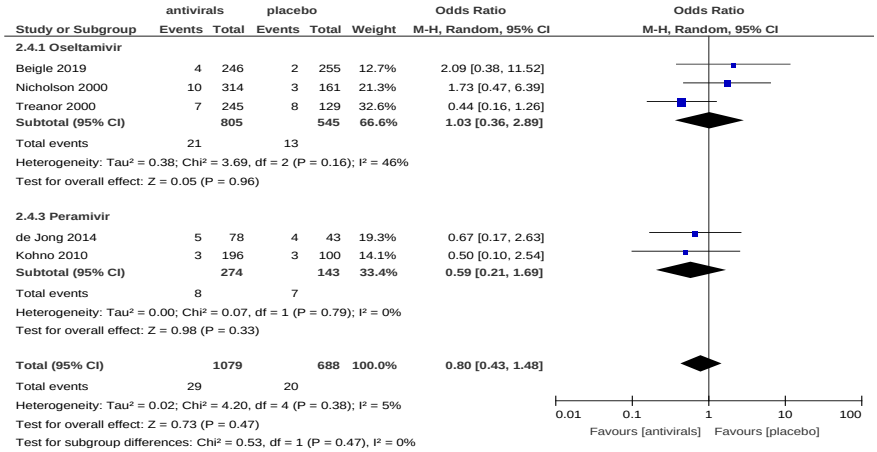
× high risk population

Additional file 4.

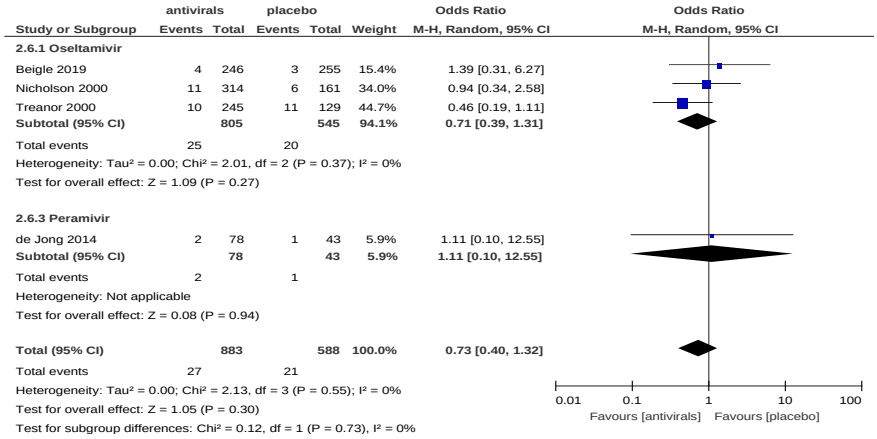
A. Pneumonia



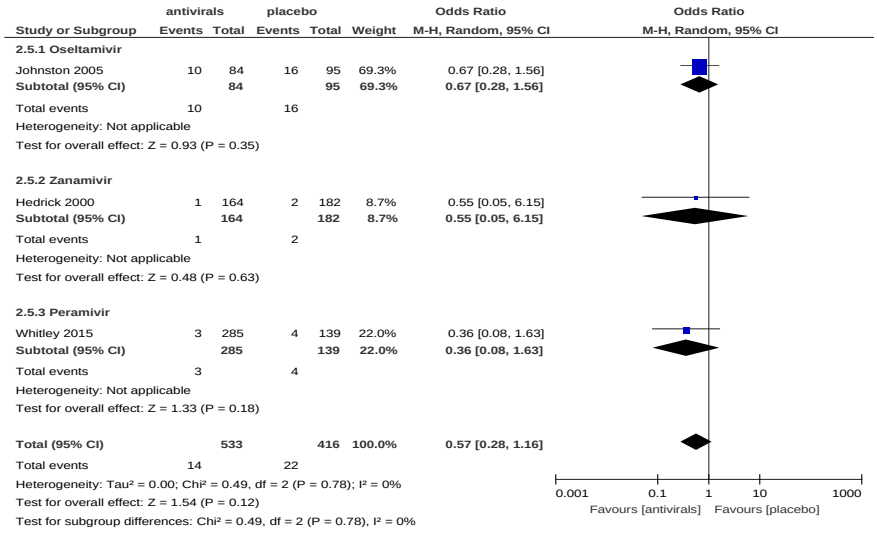
B. Bronchitis



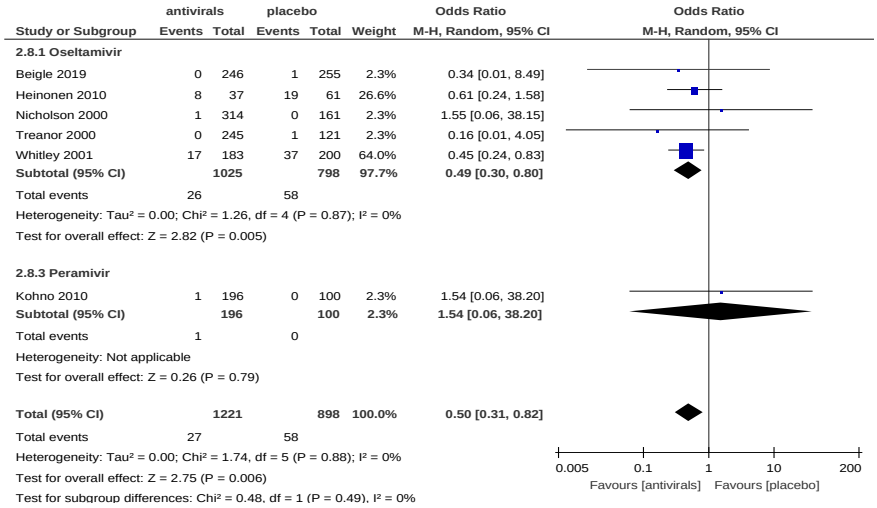
C. Sinusitis



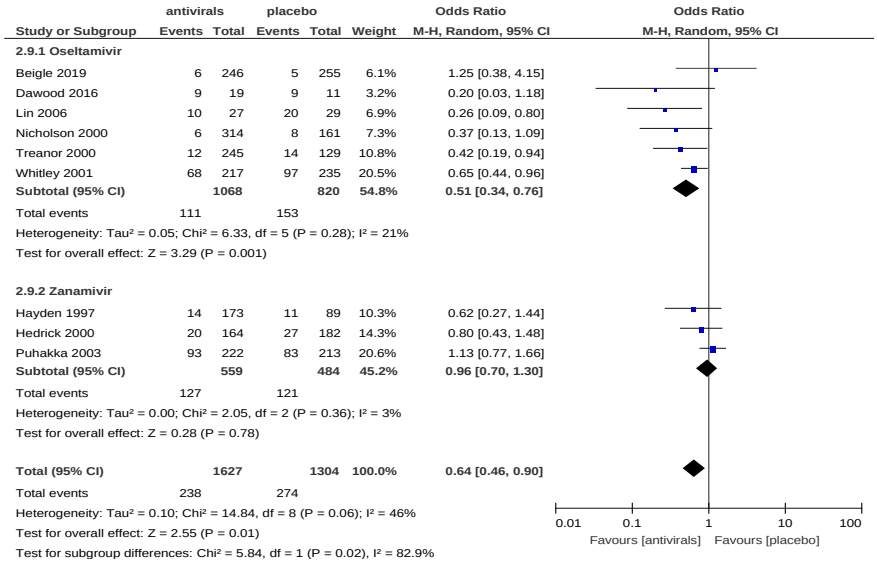
D. Asthma exacerbations



E. Acute otitis media



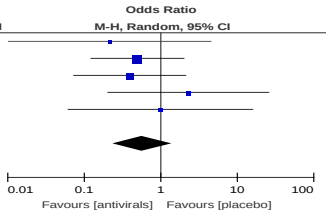
F. Antibiotic treatment



G. Hospitalizations

Study or Subgroup	antivirals Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Whitley 2001	0	217	2	235	8.5%	0.21 [0.01, 4.50]
Murphy 2000	3	262	6	263	40.2%	0.50 [0.12, 2.01]
Lin 2006	2	58	5	60	27.7%	0.39 [0.07, 2.11]
Johnston 2005	2	84	1	95	13.4%	2.29 [0.20, 25.75]
Fry 2014	1	598	1	592	10.2%	0.99 [0.06, 15.86]
Total (95% CI)		**1219**		**1245**	**100.0%**	**0.57 [0.24, 1.38]**
Total events	8		15			

Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.21)



H. Study withdrawals due to adverse events

Study or Subgroup	antivirals Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2.13.1 Oseltamivir						
Heinonen 2010	11	205	5	204	19.7%	2.26 [0.77, 6.62]
Johnston 2005	2	170	4	164	7.8%	0.48 [0.09, 2.64]
Treanor 2000	7	420	1	209	5.1%	3.53 [0.43, 28.84]
Whitley 2001	6	217	4	235	13.9%	1.64 [0.46, 5.90]
Subtotal (95% CI)		**1012**		**812**	**46.5%**	**1.66 [0.83, 3.35]**
Total events	26		14			

Heterogeneity: Tau² = 0.00; Chi² = 2.86, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.15)

2.13.2 Zanamivir						
Hayden 1997	12	273	6	144	22.7%	1.06 [0.39, 2.88]
MIST study 1998	4	227	6	228	13.9%	0.66 [0.18, 2.38]
Murphy 2000	2	262	4	263	7.8%	0.50 [0.09, 2.74]
Mäkelä 2000	2	182	0	0		Not estimable
Puhakka 2003	0	293	1	295	2.2%	0.33 [0.01, 8.24]
Subtotal (95% CI)		**1237**		**930**	**46.6%**	**0.77 [0.38, 1.54]**
Total events	20		17			

Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)

2.13.3 Peramivir						
de Jong 2014	2	264	0	134	2.5%	2.56 [0.12, 53.74]
Kohno 2010	0	196	1	100	2.2%	0.17 [0.01, 4.18]
Whitley 2015	1	285	0	139	2.2%	1.47 [0.06, 36.34]
Subtotal (95% CI)		**745**		**373**	**6.9%**	**0.89 [0.15, 5.52]**
Total events	3		1			

Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)

Total (95% CI)		**2994**		**2115**	**100.0%**	**1.11 [0.69, 1.79]**
Total events	49		32			

Heterogeneity: Tau² = 0.00; Chi² = 7.80, df = 10 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.66)
Test for subgroup differences: Chi² = 2.40, df = 2 (P = 0.30), I² = 16.8%