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Financial Conflicts of Interest and Conclusions About Neuraminidase Inhibitors for Influenza

An Analysis of Systematic Reviews

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Background: Industry funding and financial conflicts of interest may contribute to bias in the synthesis and interpretation of scientific evidence.

Objective: To examine the association between financial conflicts of interest and characteristics of systematic reviews of neuraminidase inhibitors.

Design: Retrospective analysis.

Setting: Reviews that examined the use of neuraminidase inhibitors in the prophylaxis or treatment of influenza, were published between January 2005 and May 2014, and used a systematic search protocol.

Measurements: Two investigators blinded to all information regarding the review authors independently assessed the presentation of evidence on the use of neuraminidase inhibitors as favorable or not favorable. Financial conflicts of interest were identified using the index reviews, other publications, and Web-based searches. Associations between financial conflicts of interest, favorability assessments, and presence of critical appraisals of evidence quality were analyzed.

Results: Twenty-six systematic reviews were identified, of which 13 examined prophylaxis and 24 examined treatment, accounting for 37 distinct assessments. Among assessments associated with a financial conflict of interest, 7 of 8 (88%) were classified as favorable, compared with 5 of 29 (17%) among those without a financial conflict of interest. Reviewers without financial conflicts of interest were more likely to include statements about the quality of the primary studies than those with financial conflicts of interest.

Limitations: The heterogeneity in populations and outcomes examined in the reviews precluded analysis of the contribution of selective inclusion of evidence on the discordance of the assessments made in the reviews. Many of the systematic reviews had overlapping authorship.

Conclusion: Reviewers with financial conflicts of interest may be more likely to present evidence about neuraminidase inhibitors in a favorable manner and recommend the use of these drugs than reviewers without financial conflicts of interest.

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Industry funding and author financial conflicts of interest may influence the production and synthesis of scientific evidence (1). Associations with the pharmaceutical company developing and marketing a drug have been found to influence the design of trials (2), the conduct of trials (3), and the reporting of trial results (4–7). Furthermore, financial ties and industry funding seem to result in greater rates of favorable conclusions in clinical trials examining new drugs (8–12). Fewer studies have considered the potential influence of financial conflicts of interest on the synthesis of clinical evidence in systematic reviews (13, 14).

Neuraminidase inhibitors, which are used in the prophylaxis and treatment of seasonal and pandemic influenza, have been the subject of ongoing uncertainty about their specific clinical benefits (15, 16). This is the result of not only the continuing emergence of strains with unknown drug responses but also the increasing awareness in the medical community that, until recently, its knowledge of the safety and efficacy of these drugs has been incomplete (17). Despite the abundance of clinical trials and publications on neuraminidase inhibitors, the details of many key trials had not been disclosed (18, 19). As a result, systematic reviewers analyzing and synthesizing evidence on the effectiveness of these agents have faced incomplete information, unresolved discrepancies in the data, and a high risk of publication and reporting biases among the primary clinical trials (20, 21). This prompted extensive efforts to access complete records of all published and unpublished clinical trials from manufacturers, culminating in the publication of several reviews on the basis of comprehensive clinical study reports and potentially changing the way systematic reviews will be undertaken in the future (22–27).

Reviews of neuraminidase inhibitors exhibit wide variation in their conclusions, ranging from strong endorsements of the use of these agents in the prophylaxis and treatment of influenza (28, 29) to more conservative assessments questioning the evidence on the drugs' safety and efficacy (15, 30). The reasons for this discordance in review conclusions are likely multifactorial and may be related in part to the manner in which evidence is accessed, synthesized, and presented (23, 27), both in terms of the numerical results and the authors' emphasis and interpretation (31, 32). Our aim was to determine whether there is an association between financial conflicts of interest and the favorable presentation of evidence in systematic reviews on

the use of neuraminidase inhibitors for the prophylaxis and treatment of influenza.

Methods

Data Sources

Systematic reviews were identified in PubMed, PubMed In Process, EMBASE, and the Cochrane Database of Systematic Reviews. Searches were done using the keywords "influenza," "neuraminidase inhibitors," "oseltamivir," "zanamivir," "peramivir," and "laninamivir." Articles were retrieved if the search terms appeared in the title or abstract or were included as database-specific keywords. In PubMed and EMBASE, searches were also constrained to "review" publication types. We limited our search to English-language articles published since 1 January 2005. These articles were manually reviewed to identify those that focused on the use of neuraminidase inhibitors for influenza prophylaxis or treatment (such as excluded articles primarily about drug development or other manufacturing processes). We selected all reviews that used a systematic search protocol, which we defined as the inclusion and reporting of an explicit search strategy, including reasons for subsequent exclusion of articles. The final searches were done on 26 May 2014.

Cochrane reviews are periodically updated to incorporate new evidence, and the results and conclusions are resynthesized as indicated. The authors of these reviews are typically different, and there may be differences in the methods as well as the results and language of the review. These updated reviews were included separately. Other Cochrane reviews are occasionally rewritten by a subset of the authors for publication in medical journals as abridged versions to increase dissemination. These reports have separate peer reviews and are prepared on the basis of a selection of the complete results. We considered these reviews separately as well but also did a sensitivity analysis in which they were combined with the original Cochrane reviews.

Data Extraction

Financial conflicts of interest were identified for all authors of the reviews and included affiliations with or funding from the pharmaceutical company manufacturing any of the neuraminidase inhibitors under review. We defined financial conflicts of interest as employment, the funding of grants paid to an author or an author's research group, and the funding of medical writers for the systematic review. These financial conflicts of interest were identified using information about affiliations or funding listed in the systematic reviews, as well as in any other articles published by one of the authors during the 3 years before the publication of the index systematic review. In addition, we searched authors' personal and institutional Web sites; lists of disclosures from GlaxoSmithKline (Research Triangle Park, North Carolina) and Roche Pharmaceuticals (Basel, Switzerland); and performed Web searches combining the names of the authors, drugs, and pharmaceutical companies to identify any additional information about financial relationships. Details of the specific financial conflicts of interest identified for each author are listed in **Appendix Table 1** (available at www.annals.org).

For each systematic review, we recorded whether prophylaxis or treatment was assessed, the forms of evidence to be included (such as randomized, controlled trials and observational studies), the specific clinical outcomes assessed, the populations examined, and whether meta-analyses were done. We also examined whether the reviews included information about the validity or quality of the primary literature. In particular, we recorded whether there were statements addressing nonpublication of primary studies or publication bias, including tests done by the reviewers to assess for bias in meta-analyses (such as the Egger or Begg test [33, 34]), difficulty in accessing comprehensive study data, and the prevalence or role of industry in conducting and funding the primary studies.

Data Analysis

Two investigators were provided with redacted copies of each review that did not include the reviews' authors, their affiliations, or information on financial conflicts of interest. These versions also did not contain the journal name, journal formatting, or the article's acknowledgments or references. The investigators independently evaluated the reviews and classified the prophylaxis and treatment assessments as favorable or not favorable toward the use of neuraminidase inhibitors. They were instructed to do this grading on the basis of the entirety of the review text without restriction to conclusions or recommendations made in any specific section of the review, thus allowing them to take into account the emphasis and interpretation of the authors throughout the review. The agreement between the investigators was strong at 86% (Cohen κ, 0.72; $P < 0.001$). Disagreements were resolved by a third investigator using the same redacted copies.

Descriptive analyses were done to examine the associations between financial conflicts of interest and the grading of the systematic reviews. A sensitivity analysis excluding the summary reviews was done to further examine this association. We also assessed the association between financial conflicts of interest and the inclusion of statements addressing the validity or quality of the primary evidence.

Role of the Funding Source

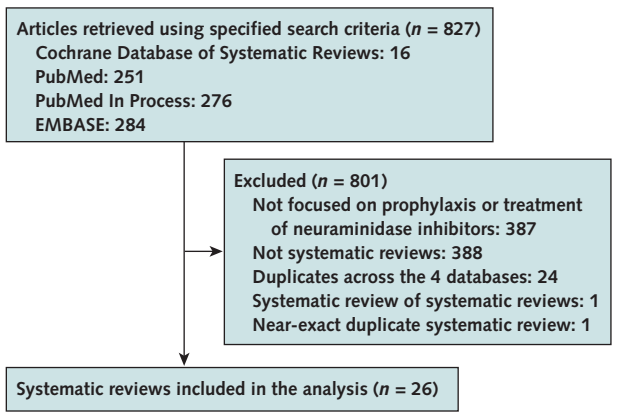
This study was funded by the Australian National Health and Medical Research Council. The funding source had no role in the design and conduct of the study, analysis of the results, or the decision to submit the manuscript for publication.

Results

We identified 827 published articles across the 4 databases using the specified search criteria, with 26 systematic reviews included in the final cohort (**Figure**). Thirteen

reviews examined prophylaxis and 24 examined treatment of influenza, accounting for 37 distinct assessments (**Appendix Table 2**, available at www.annals.org). In terms of review methods, 7 were Cochrane systematic reviews and 19 conducted and reported a meta-analysis (73%). The evidence inclusion criteria were limited to randomized, controlled trials for 14 of the systematic reviews (54%), and 5 included evidence from clinical study reports or patient-level data. The main populations examined were healthy adults (18 of 26 systematic reviews), children (13 of 26), and hospitalized patients (6 of 24). The outcome measures for prophylaxis assessments included influenza-like illness and laboratory-confirmed influenza. For the treatment assessments, the outcomes were illness duration, influenza-related complications, hospitalization, and mortality, mostly in combination. Five reviews were updates of previous Cochrane reviews, and 3 were summary reviews based on Cochrane reviews.

Figure. **Summary of evidence search and selection.**



Eligible systematic reviews included those with outcomes related to the prophylaxis or treatment of influenza.

Association Between Financial Conflicts of Interest and Favorable Assessments

Seven of the 26 systematic reviews (27%), corresponding to 8 of the 37 assessments (22%), were associated with a financial conflict of interest (**Appendix Table 1**). We identified financial conflicts of interest in publications other than the index systematic review in 2 cases, and no additional conflicts were identified on the basis of the online searches. One systematic review did not include an explicit disclosure statement, and no conflicts were identified in the additional searches.

Twelve of the 37 assessments (32%) were graded as favorable. Among the assessments pertaining to prophylaxes, 23% (3 of 13) were favorable, whereas 38% (9 of 24) of those addressing treatment supported the use of neuraminidase inhibitors (**Appendix Table 2**).

Among assessments associated with a financial conflict of interest, 7 of 8 (88%) were graded as favorable, compared with 5 of 29 (17%) among those without a financial conflict of interest. When prophylaxis and treatment assessments were considered separately, those with a financial conflict of interest were more likely to be graded as favorable in both cases: 2 of 2 (100%) versus 1 of 11 (9%) systematic reviews with financial conflicts of interest were graded as favorable for prophylaxis, and 5 of 6 (83%) versus 4 of 18 (22%) were graded as favorable for treatment. These results did not change substantially in the sensitivity analysis excluding the summary reviews from the analysis (2 of 2 [100%] systematic reviews with financial conflicts of interest were graded as favorable for prophylaxis vs. 1 of 8 [13%] without financial conflicts of interest, and 5 of 6 [83%] vs. 4 of 15 [27%] were graded as favorable for treatment).

Among the systematic reviews that were graded as favorable, there were 3 disconnected groups of authors with financial conflicts of interest and 4 other groups of authors that were not connected by coauthorship to systematic reviews with relevant financial conflicts of interest. Among the systematic reviews that were not graded as favorable, most (10 of 16 [63%]) belonged to a single connected group of coauthors, and these were mostly Cochrane systematic reviews or the related summary reviews.

Inclusion and Exclusion of Primary Evidence

The heterogeneity in the types of studies, populations, and outcomes included in the reviews precluded an analysis of the selection of individual studies in the systematic reviews. When examining the inclusion and exclusion of evidence for the subset of reviews that studied duration of symptoms using only evidence from randomized, controlled trials, we found no unexplained exclusions of available primary clinical trials.

Validity and Quality of Primary Clinical Studies

Fifteen systematic reviews addressed the issue of publication bias, including finding evidence of publication bias, identifying unpublished results, or describing concerns for publication bias among the primary clinical studies supporting the review (**Table** and **Appendix Table 3**, available at www.annals.org). Reviewers without financial conflicts of interest more often included a statement about publication bias (15 of 19 [79%]) than reviewers with financial conflicts of interest (1 of 7 [14%]). Ten systematic reviews addressed difficulties accessing comprehensive study data, and 8 described the prevalence of industry funding in the primary studies. None of these systematic reviews included authors with financial conflicts of interest.

Discussion

The wide range of assessments on the effectiveness of neuraminidase inhibitors presented in systematic reviews points to potential bias in the synthesis and interpretation of primary evidence. We found that systematic reviews by

Table. **Consideration of Validity and Quality of Primary Clinical Studies in Systematic Reviews of Neuraminidase Inhibitors**

Variable	Reviews Without a Financial Conflict of Interest (n = 19)	Reviews With a Financial Conflict of Interest (n = 7)
Publication bias among clinical studies	15	1
Access to comprehensive study data	10	0
Industry support of clinical studies	8	0

authors with financial conflicts of interest were more likely to report favorably on the clinical use of neuraminidase inhibitors in the prophylaxis and treatment of influenza. Reviewers with such conflicts were also less likely to address issues with the underlying primary clinical evidence, such as publication bias and the lack of access to comprehensive study data.

Our study is the first to examine the potential influence of financial conflicts of interest on the presentation of evidence in systematic reviews of neuraminidase inhibitors. Strengths of our study include the comprehensive analysis of all systematic reviews on this topic; the strong agreement between 2 independent, blinded appraisals of the review assessments; and the extensive evaluation of financial conflicts of interest beyond those reported in the index publication. Few studies have examined the effect of industry funding and financial conflicts of interest on conclusions in systematic reviews. A study matching Cochrane systematic reviews with industry-supported reviews showed that industry-supported reviews were more likely to conclude favorably (14), and another found that systematic reviews with sponsorship from the food industry were less likely to find an association between sugar-sweetened beverages and weight gain than systematic reviews without such support (13). The results of these studies are aligned with ours, indicating that financial conflicts of interest are associated with product assessments favorable to the sponsors involved.

The systematic reviews ranged from those supporting the efficacy of neuraminidase inhibitors for widespread prophylaxis and early treatment and advocating for national stockpiling (35–37) to others recommending that these drugs not be used in routine seasonal prophylaxis, those reporting no evidence that they reduce the risk for hospitalization and complications, and those discouraging stockpiling (**Appendix Tables 4** and **5**, available at www.annals.org) (22, 38, 39). Factors that may influence the conclusions drawn in systematic reviews include the design of the review, the patient populations and outcomes assessed, the selective inclusion of primary evidence (40), the critical appraisal of evidence quality and provenance (41), and the formulation of conclusions and recommendations on the basis of subjective interpretations of the results. The tone, emphasis, and interpretation provided by the authors may also influence the message that is conveyed (32, 42, 43). In the case of neuraminidase inhibitors, it is possible that reviewer opinions on the quality and validity of the underlying primary evidence are particularly influential in developing conclusions. This is reflected in part by our results, which show that authors without financial conflicts of interest were more likely to address potential quality issues than authors with such conflicts.

Systematic reviews represent an important source of summary evidence, and there are many downstream effects to the conflicting assessments on the effectiveness of neuraminidase inhibitors. If the benefits of neuraminidase inhibitors are eventually found to have been inflated, millions of patients will have been unnecessarily exposed to drugs that may be of little or no benefit. The uncertainty in the evidence may have led to poor translation of evidence into practice—slow uptake in specific populations and for certain presentations in which the use of neuraminidase inhibitors is beneficial. Global stockpiling of antivirals was recommended by a panel from the World Health Organization in 2002, and in 2009, governments around the world spent $6.9 billion building stockpiles of oseltamivir (44), an investment that remains poorly supported by available clinical evidence.

The pharmaceutical companies marketing neuraminidase inhibitors have made important contributions to the clinical data available for this drug class, and most of the primary evidence included in the systematic reviews is based on industry-sponsored clinical trials. Researchers have argued that industry-sponsored research should not be published in journals (45), and the recognition of a persistent bias in systematic reviews may support this stance. However, this is likely to be inefficient in an environment where most systematic reviews are out of date (46), and the persons who currently have the best access to comprehensive trial results are directly affiliated or financially tied to the companies undertaking those trials. As an alternative, systematic reviews would benefit from greater availability of full clinical study reports (18, 19), critical appraisal of the selection of evidence and the clinical outcomes assessed, and closer monitoring of the role of industry collaborators in interpreting results and formulating conclusions (32).

One limitation of our study is that we could not determine which of the assessments about the efficacy of neuraminidase inhibitors is most accurate. It is possible that authors without financial conflicts of interest were predisposed to a less favorable view of the evidence because of existing controversies and uncertainties around the primary evidence. We were also unable to determine which factors contributed to the different conclusions between reviews written by authors with and without financial conflicts of interest. Although authors with financial conflicts of interest may participate in Cochrane systematic reviews, none of the authors with financial conflicts of interest examined

here chose to conduct a Cochrane review. Cochrane systematic reviews follow strict procedures (including presenting relevant measures of publication bias and funding of included trials), and it is possible that these methods contributed to the differences in the conclusions found between reviewers with and without financial conflicts of interest. Another limitation of our study is that the heterogeneity of the populations and outcomes in the systematic reviews precluded an analysis on the unwarranted exclusion of primary evidence as a source of bias in review conclusions.

There are persistent disagreements between systematic reviewers on the clinical benefits of neuraminidase inhibitors in the prophylaxis and treatment of influenza. Reviewers with financial conflicts of interest are more likely to author systematic reviews that are favorable to the use of neuraminidase inhibitors, suggesting that industry influence may have contributed to the inconsistent conclusions. The reporting of financial conflicts of interest in systematic reviews may not be sufficient to mitigate the effects of industry affiliations, and further measures may be necessary to ensure that industry collaborations do not compromise the scientific evidence.

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51. **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;65:1330-46. [PMID: 20488984] doi:10.1093/jac/dkq158
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53. **Jackson RJ, Cooper KL, Tappenden P, Rees A, Simpson EL, Read RC, et al.** Oseltamivir, zanamivir and amantadine in the prevention of influenza: a systematic review. J Infect. 2011;62:14-25. [PMID: 20950645] doi:10.1016/j.jinf.2010.10.003
54. **Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A, et al; PRIDE Consortium Investigators.** 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;2:395-404. [PMID: 24815805] doi:10.1016/S2213-2600(14)70041-4
55. **Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A.** Antivirals for influenza in healthy adults: systematic review. Lancet. 2006;367:303-13. [PMID: 16443037]
56. **Shun-Shin M, Thompson M, Heneghan C, Perera R, Harnden A, Mant D.** Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. BMJ. 2009;339:b3172. [PMID: 19666987] doi:10.1136/bmj.b3172
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59. **Jagannath VA, Asokan GV, Fedorowicz Z, Singaram JS, Lee TW.** Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. Cochrane Database Syst Rev. 2010:CD008139. [PMID: 20238363] doi:10.1002/14651858.CD008139.pub2
60. **Wang K, Shun-Shin M, Gill P, Perera R, Harnden A.** Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev. 2012;1:CD002744. [PMID: 22258949] doi:10.1002/14651858.CD002744.pub3
61. **Wang K, Shun-Shin M, Gill P, Perera R, Harnden A.** Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database Syst Rev. 2012;4:CD002744. [PMID: 22513907] doi:10.1002/14651858.CD002744.pub4
62. **Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al.** Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med. 2012;156:512-24. [PMID: 22371849] doi:10.7326/0003-4819-156-7-201204030-00411
63. **Jagannath VA, Asokan GV, Fedorowicz Z, Lee TW.** Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. Cochrane Database Syst Rev. 2014;2:CD008139. [PMID: 24515341] doi:10.1002/14651858.CD008139.pub3
64. **Freemantle N, Shallcross LJ, Kyte D, Rader T, Calvert MJ.** Oseltamivir: the real world data. BMJ. 2014;348:g2371. [PMID: 24811409] doi:10.1136/bmj.g2371
65. **Nicholson KG, Thompson CI, Klap JM, Wood JM, Batham S, Newman RW, et al.** Safety and immunogenicity of whole-virus, alum-adjuvanted whole-virus, virosomal, and whole-virus intradermal influenza A/H9N2 vaccine formulations. Vaccine. 2009;28:171-8. [PMID: 19799843] doi:10.1016/j.vaccine.2009.09.103
66. **Jennings LC, Monto AS, Chan PK, Szucs TD, Nicholson KG.** Stockpiling prepandemic influenza vaccines: a new cornerstone of pandemic preparedness plans. Lancet Infect Dis. 2008;8:650-8. [PMID: 18922487] doi:10.1016/S1473-3099(08)70232-9

Appendix Table 1. **Financial Conflicts of Interest Among Authors of the Systematic Reviews**

Author, Year (Reference)	Source of Financial Conflict of Interest Information	Financial Conflict of Interest Type and Recipient	Year	Sponsor
Postma et al, 2008 (48)				
Postma MJ	Postma et al, 2008 (48)	Writing, Postma	2008	Roche
Beardsworth P	Postma et al, 2008 (48)	Employment, Beardsworth	2008	Roche
Burch et al, 2009 (49)				
Nicholson KG	Nicholson et al, 2009 (65)	Funding, University Hospitals of Leicester	2009	Roche, Gilead
Nicholson KG	Burch et al, 2009 (57)	Funding, Department of Infection, Immunity, and Inflammation, University of Leicester	2009	Roche
Nicholson KG	Jennings et al, 2008 (66)	Funding, Department of Infectious Disease and Tropical Medicine, Leicester Royal Infirmary	2008	Roche
Burch et al, 2009 (57)				
Nicholson KG	Burch et al, 2009 (57)	Funding, Department of Infection, Immunity, and Inflammation, University of Leicester	2009	Roche
Nicholson KG	Nicholson et al, 2009 (65)	Funding, University Hospitals of Leicester	2009	Roche, Gilead
Nicholson KG	Jennings et al, 2008 (66)	Funding, Department of Infectious Disease and Tropical Medicine, Leicester Royal Infirmary	2008	Roche
Jackson et al, 2011 (53)				
Nicholson KG	Burch et al, 2009 (57)	Funding, Department of Infection, Immunity, and Inflammation, University of Leicester	2009	Roche
Nicholson KG	Nicholson et al, 2009 (65)	Funding, University Hospitals of Leicester	2009	Roche, Gilead
Muthuri et al, 2013 (36)				
Muthuri SG	Muthuri et al, 2013 (36)	Funding, Muthuri	2013	Roche
Muthuri SG	Muthuri et al, 2013 (36)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK
Venkatesan S	Muthuri et al, 2013 (36)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK
Myles PR	Muthuri et al, 2013 (36)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK
Nguyen-Van-Tam JS	Beck et al, 2013 (37)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK, Roche
Beck et al, 2013 (37)				
Nguyen-Van-Tam JS	Beck et al, 2013 (37)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK, Roche
Puleston R	Beck et al, 2013 (37)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK, Roche
Puleston R	Beck et al, 2013 (37)	Funding, Puleston	2013	GSK
Beck CR	Beck et al, 2013 (37)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK, Roche
Muthuri et al, 2014 (54)				
Muthuri SG	Muthuri et al, 2014 (54)	Funding, Muthuri	2014	Roche
Myles PR	Muthuri et al, 2014 (54)	Funding, Myles	2014	Roche
Booy R	Muthuri et al, 2014 (54)	Funding, Booy	2014	GSK, Roche
Nguyen-Van-Tam JS	Muthuri et al, 2014 (54)	Funding, Nguyen-Van-Tam	2014	GSK
Nguyen-Van-Tam JS	Beck et al, 2013 (37)	Funding, University of Nottingham Health Protection and Influenza Research Group	2013	GSK, Roche

GSK = GlaxoSmithKline.

Appendix Table 2. **Characteristics of Systematic Reviews Examining Prophylaxis and Treatment Outcomes for Neuraminidase Inhibitors**

Variable	Graded as Favorable							
	Matheson et al, 2007 (47)	Postma et al, 2008 (48)	Burch et al, 2009 (49)	Khazeni et al, 2009 (35)	Falagas et al, 2010 (50)	Falagas et al, 2010 (51)	Mosby et al, 2011 (52)	Jackson et al, 2011 (53)
Neuraminidase inhibitor								
Zanamivir	●		●	●	●	●	●	●
Oseltamivir	●	●	●	●	●	●	●	●
Systematic review design								
Cochrane systematic review	●							
Includes a meta-analysis	●		●	●		●		●
Evidence inclusion								
Published randomized, controlled trials	●		●	●		●		●
Published observational studies					●		●	
Pharmacoeconomic studies		●						
Clinical study reports or patient-level data								
Prophylaxis outcomes								
Influenza-like illness	●	NA	NA		NA	NA	NA	
Confirmed influenza	●	NA	NA	●	NA	NA	NA	●
Treatment outcomes								
Duration of symptoms	●	●	●	NA				NA
Complications	●	●	●	NA		●	●	NA
Hospitalization	●	●	●	NA			●	NA
Mortality			●	NA	●	●	●	NA
Patient populations								
Healthy adults		●	●	●	●	●		●
Children	●	●			●			●
Hospitalized patients		●		NA	●		●	NA
Other populations†		●	●	●	●	●	●	●
Updates and summary reviews								
Update of previous review								
Summary review‡								
Shared authors on ≥2 other systematic reviews	●		●					●
Quality assessments								
Statement on publication bias	●			●	●	●		
Statement on access to study data	●			●				
Statement on industry support of studies				●				
Efficacy assessments								
Graded as favorable for treatment	●	●	●	NA	●	●	●	NA
Graded as favorable for prophylaxis		NA	NA	●	NA	NA	NA	●
Financial conflicts of interest								
Financial conflict of interest present		●	●					●

NA = not applicable.
* Reviewers could not undertake meta-analyses because no evidence was identified.
† Included pregnant women, patients with cystic fibrosis, elderly persons, and populations with underlying conditions.
‡ Prepared on the basis of reviews published in Cochrane Database of Systematic Reviews.

Appendix Table 2—**Continued**

Graded as Favorable			Not Graded as Favorable					
Beck et al, 2013 (37)	Muthuri et al, 2013 (36)	Muthuri et al, 2014 (54)	Jefferson et al, 2006 (55)	Shun-Shin et al, 2009 (56)	Jefferson et al, 2009 (39)	Burch et al, 2009 (57)	Jefferson et al, 2010 (58)	Jagannath et al, 2010 (59)
●	●	●	●	●	●	●	●	●
●	●	●	●	●	●	●	●	●
							●	●
●	●	●	●	●	●	●	●	NA*
●			●	●	●	●	●	●
●	●							
		●						
	NA	NA	●		●	NA	●	NA
●	NA	NA	●	●	●	NA	●	NA
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●	●	●	●	●	●	●	●	
	●			●	●		●	
				●	●		●	
●	NA	NA				NA		NA
●	●	●				●		

Appendix Table 2—**Continued**

Not Graded as Favorable								
Jefferson et al, 2012 (20)	Wang et al, 2012 (60, 61)	Hsu et al, 2012 (62)	Ebell et al, 2013 (38)	Jagannath et al, 2014 (63)	Freemantle et al, 2014 (64)	Heneghan et al, 2014 (24)	Jefferson et al, 2014 (22)	Jefferson et al, 2014 (23)
●	●	●		●		●		●
●	●	●	●	●	●		●	●
●	●			●				●
●	●		●	NA*		●	●	●
	●		●	●				
		●			●			
●						●	●	●
●		NA	NA	NA	NA	●	●	●
●	●	NA	NA	NA	NA	●	●	●
●	●	●	●	●		●	●	●
●	●	●	●	●	●	●	●	●
●	●	●	●	●		●	●	●
		●			●			●
●		●	●		●	●	●	●
●	●	●			●	●	●	●
		●						
		●		●	●			
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						●	●	
●	●					●	●	●
●	●	●	●		●	●	●	●
●	●					●	●	●
●	●	●	●		●	●		●
		NA	NA	NA	NA			

Appendix Table 3. Statements Addressing the Validity of Primary Studies

Author, Year (Reference)	Publication Bias or Nonpublication of Primary Studies	Incomplete Access to Comprehensive Study Data	Industry Support of Primary Studies
Jefferson et al, 2006 (55)	NA	NA	NA
Matheson et al, 2007 (47)	"We identified several negative results reported by regulatory bodies as part of drug licensing and approval assessments that had, at least initially, not been published in peer-reviewed journal articles or conference presentations."	"In general, both Roche and GlaxoSmithKline were willing to supply conference abstracts/posters and references to published data but (with the exception of a number of clarifications by Roche) would not provide re-analyses or additional data."	NA
Postma et al, 2008 (48)	NA	NA	NA
Burch et al, 2009 (57)	NA	NA	NA
Burch et al, 2009 (49)	NA	NA	NA
Khazeni et al, 2009 (35)	"Indeed, although our analyses for publication bias are difficult to interpret in light of the small sample sizes, they suggest missing data."	"Although we performed thorough literature searches, U.S. Food and Drug Administration requirements for disclosure of clinical trial data were instituted many years after the discovery of oseltamivir and zanamivir."	"All studies were sponsored by pharmaceutical companies, potentially increasing bias."
Shun-Shin et al, 2009 (56)	"Although our search was comprehensive and builds on previous Cochrane search strategies, important negative findings might not have been published beyond the conference abstract stage."	"Unable to access data (n=1)." "Because of inadequate reporting of trial data and heterogeneity of the studies we were unable to pool results."	NA
Jefferson et al, 2010 (58)	"We are unable to assess the size and direction of the obvious bias in the treatment data set due to the non-publication or partial publication of eight trials, as the data provided to us by Roche are insufficient to fill the gaps in our understanding of the population, methods and results of the studies."	"Numerous inconsistencies detected in the available evidence, followed by an inability to adequately access the data, has undermined confidence in our previous conclusions for oseltamivir."	NA
Jefferson et al, 2009 (39)	"It is possible that there is a publication bias, especially as we know of eight trials that are unpublished and inaccessible. We have not undertaken a funnel plot because there are only three trials .... and so the issue of publication bias remains unresolved."	"We were unable to gain the same access to data from the European Medicines Agency."	NA
Falagas et al, 2010 (51)	"Publication bias may also have led to a relatively high reported mortality in this review."	NA	NA
Falagas et al, 2010 (50)	"Publication and language biases may also have influenced our findings, whereas the use of the Jadad score as a method of assessment of the methodological quality of the included trials may raise considerations."	NA	NA
Jagannath et al, 2010 (59)	NA	NA	NA
Jackson et al, 2011 (53)	NA	NA	NA
Mosby et al, 2011 (52)	NA	NA	NA
Jefferson et al, 2012 (20)	"In view of the unresolved discrepancies in the data presented in published trial reports and of the substantial risk publication bias in this area, we elected not to use data from journal articles."	"The majority of modules in clinical study reports were inaccessible to us and we were therefore unable to complete the review in some of its most important aspects, such as serious harms."	"All the studies were sponsored by manufacturers of NIs."
Hsu et al, 2012 (62)	"Publication bias was a concern because large studies had for-profit funding and were weighted heavily in analyses."	NA	"Substantial reporting and publication bias may exist for several of the evaluated outcomes (in particular, complications) because the studies were funded by for-profit organizations."
Wang et al, 2012 (60, 61)	"Whether these omissions represent true publication bias (failure to publish negative or null results) or time-lag bias (trials with positive results are published more quickly than trials with negative or null results) is not clear, although the latter is well known to exaggerate treatment effects in early meta-analyses."	"We were unable to pool these data from different studies because we did not have access to individual patient data."	"All nine of our included studies received financial support from pharmaceutical companies."
Muthuri et al, 2013 (36)	"For some of the outcomes we found evidence of publication bias, which may have overestimated the observed pooled effect."	NA	NA

Continued on following page

Appendix Table 3—**Continued**

Author, Year (Reference)	Publication Bias or Nonpublication of Primary Studies	Incomplete Access to Comprehensive Study Data	Industry Support of Primary Studies
Beck et al, 2013 (37)	NA	NA	NA
Ebell et al, 2013 (38)	"We are concerned about the failure to publish the results of large, adequately powered RCTs in peer reviewed journals."	NA	"In addition, five of the six authors were employees or paid consultants of the manufacturer. This type of direct involvement by the sponsor has been shown to increase the likelihood of bias and the reporting of results favourable to the manufacturer."
Muthuri et al, 2014 (54)	NA	NA	NA
Jagannath et al, 2014 (63)	NA	NA	NA
Freemantle et al, 2014 (64)	"Their failure to publish the overall results is evidence of publication bias."	NA	"The studies by Blumentals and colleagues (2007) and Greene and colleagues (2013) both point towards oseltamivir reducing neuropsychiatric events, although only Blumentals is statistically significant. Blumentals studied staff employed by Roche and Thompson Healthcare, and the work of Greene and colleagues was sponsored by America's Health Insurance Plans (AHIP) under contract from the Centers for Disease Control and Prevention (CDC)."
Heneghan et al, 2014 (24)	"However, these conclusions have been undermined by publication bias, missing data, limitations in the design of the studies, and the conduct and reporting of trials."	"Access to evidence has proved crucial in determining the effects of zanamivir, and early decision making on regulatory approval has been hampered by a lack of access to the trial data."	"It is also worth noting that to date there has been no publically funded trial of zanamivir, which given that we know manufactured funded trials overstate treatment effects is somewhat puzzling, given the extensive use and stockpiling of this drug."
Jefferson et al, 2014 (22)	"Because of discrepancies between published and unpublished reports of the same trials, we decided to include only those trials for which we had unabridged clinical study reports. "Examples of benefits in accessing full clinical study reports include assessment of reliability of some outcome definitions (for example, "pneumonia"), a considerable amount of data on potential harms, and avoided reliance of conclusions on published papers, which themselves may have hitherto unseen unpublished material included."	"In the first phase we did not have the full clinical study reports promised by Roche, but instead had 15 incomplete clinical study reports from EMA."	NA
Jefferson et al, 2014 (23)	"This shift in our data synthesis paradigm was made necessary by the numerous and documented discrepancies between regulatory and published evidence and by the sizeable risk of publication bias of the oseltamivir trial programme."	"We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled, phase III treatment trials of oseltamivir have never been published."	"All reports in our review were sponsored by the manufacturers. It is known that published studies sponsored by the pharmaceutical industry are more likely to have outcomes favouring the sponsor compared to studies which have other sponsors (Lexchin 2003; Lundh 2012). As the evidence relates to published studies, we do not know whether the findings are applicable to clinical study reports."

EMA = European Medicines Agency; NA = not applicable; NI = neuraminidase inhibitor; RCT = randomized, controlled trial.

Appendix Table 4. **Conclusions and Recommendations About the Clinical Use of Neuraminidase Inhibitors From the Abstracts of Systematic Reviews**

Systematic Review	Conclusion/Recommendation
Graded as favorable	
Muthuri et al, 2014 (54) (conflict of interest)	"We advocate early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection."
Beck et al, 2013 (37) (conflict of interest)	"[NIs] should be deployed during a future pandemic for either post-exposure prophylaxis or treatment depending on national policy considerations and logistics."
Jackson et al, 2011 (53) (conflict of interest)	"Oseltamivir was effective in preventing symptomatic laboratory-confirmed influenza (SLCI) in seasonal prophylaxis in healthy adults and at-risk elderly subjects and in post-exposure prophylaxis within households of mixed composition. Post-exposure prophylaxis using oseltamivir for paediatric contacts was observed to prevent SLCI. Zanamivir prevented SLCI in seasonal prophylaxis in healthy adults, at-risk adults and adolescents and in post-exposure prophylaxis within mixed households, with a trend for seasonal and post-exposure preventative effects in elderly subjects."
Burch et al, 2009 (49) (conflict of interest)	"Despite some concerns, the use of NIs in at-risk populations appeared to be a cost-effective approach for the treatment of influenza."
Postma et al, 2008 (48) (conflict of interest)	"Despite the range of values assumed for key probabilities such as the diagnostic certainty of influenza among people presenting with influenza-like illness, and how much work time is lost due to illness in healthy adults, base-case analyses consistently showed oseltamivir treatment to be cost effective or even cost saving for the four population groups studied, a conclusion that is in-line with previous reviews on this topic."
Mosby et al, 2011 (52)	"Pregnant women who received delayed treatment with neuraminidase inhibitors or who had additional risk factors were more likely to develop severe disease."
Falagas et al, 2010 (51)	"NIs seem to be effective in reducing total influenza-related complications in otherwise healthy and high-risk patients, and have an acceptable safety profile."
Falagas et al, 2010 (50)	"Comparative data from the largest included study (involving 1088 patients) indicated that administration of antivirals within 2 days from symptom onset was significantly associated with reduced mortality ($P < 0.001$)."
Khazeni et al, 2009 (35)	"Extended-duration zanamivir and oseltamivir chemoprophylaxis seems to be highly efficacious for preventing symptomatic influenza among immunocompetent white and Japanese adults."
Matheson et al, 2007 (47) (treatment)	"Neuraminidase inhibitors are effective in shortening illness duration in healthy children with influenza, but efficacy in 'at risk' children remains to be proven."
Graded as not favorable	
Burch et al, 2009 (57) (conflict of interest)	"In view of the advantages and disadvantages of different management strategies for controlling seasonal influenza in healthy adults recommending the use of antiviral drugs for the treatment of people presenting with symptoms is unlikely to be the most appropriate course of action."
Jefferson et al, 2014 (22)	"We believe these findings provide reason to question the stockpiling of oseltamivir, its inclusion on the WHO list of essential drugs, and its use in clinical practice as an anti-influenza drug."
Jefferson et al, 2014 (23)	"Our findings do not support the stockpiling of NIs, nor oseltamivir's inclusion in the WHO's list of essential drugs."
Heneghan et al, 2014 (24)	"Based on a full assessment of all trials conducted, zanamivir reduces the time to symptomatic improvement in adults (but not in children) with influenza-like illness by just over half a day, although this effect might be attenuated by symptom relief medication."
Jagannath et al, 2014 (63)	"The effects of NIs for influenza in people with CF are unclear."
Ebell et al, 2013 (38)	"There is no evidence that oseltamivir reduces the likelihood of hospitalization, pneumonia or the combined outcome of pneumonia, otitis media and sinusitis in the ITT population."
Hsu et al, 2012 (62)	"Therapy with oral oseltamivir and inhaled zanamivir may provide a net benefit over no treatment of influenza. However, as with the randomized trials, the confidence in the estimates of the effects for decision making is low to very low."
Wang et al, 2012 (60, 61)	"The benefit of oseltamivir and zanamivir in preventing the transmission of influenza in households is modest and based on weak evidence."
Jefferson et al, 2012 (20)	"We found a high risk of publication and reporting biases in the trial programme of oseltamivir."
Jagannath et al, 2010 (59)	"However, the question of the safety and effectiveness of neuraminidase inhibitors for treating influenza in people with cystic fibrosis remains unanswered."
Jefferson et al, 2010 (58)	"Trials are urgently needed to test whether NIs are more effective than symptomatic treatment and hygiene and barrier measures to interrupt influenza transmission in healthy adults."
Shun-Shin et al, 2009 (56)	"Neuraminidase inhibitors provide a small benefit by shortening the duration of illness in children with seasonal influenza and reducing household transmission. They have little effect on asthma exacerbations or the use of antibiotics."
Jefferson et al, 2009 (39)	"Neuraminidase inhibitors have modest effectiveness against the symptoms of influenza in otherwise healthy adults. The drugs are effective postexposure against laboratory confirmed influenza, but this is a small component of influenza-like illness, so for this outcome neuraminidase inhibitors are not effective."
Matheson et al, 2007 (47) (prophylaxis)	"Neuraminidase inhibitors are effective in shortening illness duration in healthy children with influenza, but efficacy in 'at risk' children remains to be proven. Oseltamivir is also effective in reducing the incidence of secondary complications, and may be effective for influenza prophylaxis."
Jefferson et al, 2006 (55)	"Because of their low effectiveness, neuraminidase inhibitors should not be used in seasonal influenza control and should only be used in a serious epidemic or pandemic alongside other public-health measures."

CF = cystic fibrosis; ITT = intention-to-treat; NI = neuraminidase inhibitor; WHO = World Health Organization.

Appendix Table 5. **Conclusions and Recommendations About the Clinical Use of Neuraminidase Inhibitors From the Discussions of Systematic Reviews**

Systematic Review	Conclusion/Recommendation
Graded as favorable	
Muthuri et al, 2014 (54) (conflict of interest)	"Treatment guidance policies should increase emphasis on early empirical neuraminidase inhibitor treatment of adult patients admitted to hospital after presenting with proven or clinically suspected influenza A H1N1pdm09 virus infection. However, most adult patients with suspected or confirmed influenza are not admitted to hospital within 48 h of illness onset. Therefore, the implications of these findings, although based on patients admitted to hospital with influenza A H1N1pdm09, encourage early initiation of neuraminidase inhibitor treatment in outpatients who are appreciably unwell with suspected or confirmed influenza, or at increased risk of complications, including those with influenza A H3N2 or influenza B."
Beck et al, 2013 (37) (conflict of interest)	"However, preparedness plans should consider the solid evidence for the preventive efficacy of household-based post-exposure prophylaxis with NAIs; this control measure may not suit all national settings, but clearly possesses significant utility in reducing secondary cases within households when efficiently implemented."
Muthuri et al, 2013 (36) (conflict of interest)	"Nevertheless, our finding of a 65% mortality reduction in early treated versus untreated patients suggests a meaningful public health benefit, of relevance to pandemic policy-makers, because it is more likely that untreated cases were less severe rather than more severe and the true effect may therefore have been underestimated. If this is so, pandemic preparedness policies need to emphasize not only the issue of appropriate NAI stockpiling but also practical mechanisms for ensuring easy and early access to treatment during a pandemic."
Jackson et al, 2011 (53) (conflict of interest)	"Oseltamivir was demonstrated to prevent SLCI in seasonal prophylaxis in healthy adults and at-risk elderly subjects and in post-exposure prophylaxis within households of mixed composition. Post-exposure prophylaxis using oseltamivir for paediatric contacts was also shown to be effective in preventing influenza. Evidence relating to the efficacy of zanamivir in preventing SLCI was observed in trials of seasonal prophylaxis in healthy adults, at-risk adults and adolescents, and in post-exposure prophylaxis in households of mixed composition, with a trend for seasonal and post-exposure preventative effects among elderly subjects."
Burch et al, 2009 (49) (conflict of interest)	"This review showed that treatment with zanamivir or oseltamivir, when compared with placebo, generally reduced the median duration of symptoms and median time to return to normal activity across all subgroups."
Postma et al, 2008 (48) (conflict of interest)	"Despite the range of values assumed for key probabilities such as the diagnostic certainty of influenza among people presenting with ILI, and how much work time is lost due to illness in healthy adults, base-case analyses generally showed oseltamivir treatment to be cost effective or even cost saving and the findings were consistent across the four population groups that were studied (healthy adults, children, the elderly and high-risk groups)."
Mosby et al, 2011 (52)	"Treatment up to 4 days after symptom onset, ideally within 48 hours, confers decreased risk of severe disease and death. Although safety of oseltamivir in pregnancy has not been clearly established, the benefits of treatment appear to outweigh the risks."
Falagas et al, 2010 (50)	"Nevertheless, the severity of the disease in patients in need of hospitalisation probably mandates the use of available specific antivirals."
Falagas et al, 2010 (51)	"Taking all the above into consideration, NIs seem to be effective in reducing influenza complications in both low- and high-risk patients, while they also seem to have an acceptable safety profile."
Khazeni et al, 2009 (35)	"With these cautions, zanamivir can be used in immunocompetent adults without obstructive lung disease to decrease the risk for symptomatic influenza illness when extended-duration chemoprophylaxis against seasonal influenza is needed, and it can be stockpiled to distribute to these individuals for chemoprophylaxis against pandemic influenza."
Matheson et al, 2007 (47) (treatment)	"If near-patient testing is available and economic resources permit, and provided that therapy can be commenced within 48 hours of the start of the illness, oseltamivir may be considered for the treatment of children aged 1 to 12 years with influenza infection."
Graded as not favorable	
Burch et al, 2009 (57) (conflict of interest)	"Both zanamivir and oseltamivir reduce the time to symptom alleviation in both healthy adult and at-risk populations. Despite the statistical significance of the results, the clinical value of reducing symptom duration by between half a day and 1 day is debatable, particularly in otherwise healthy adults."
Jefferson et al, 2014 (23)	"Based on these findings there appears to be no evidence for patients, clinicians or policy-makers to use these drugs to prevent serious outcomes, both in annual influenza and pandemic influenza outbreaks. Practice recommendations and drug labelling needs to be changed to reflect these findings."
Jefferson et al, 2014 (22)	"We believe these findings provide reason to question the stockpiling of oseltamivir, its inclusion on the WHO list of essential drugs, and its use in clinical practice as an anti-influenza drug."
Heneghan et al, 2014 (24)	"However, in the absence of a clear definition of bronchitis in the trials, zanamivir is no more effective in relieving symptoms than commonly used over the counter symptomatic drugs (such as paracetamol or NSAIDs). Based on the findings of this review, we do not believe further clinical trials of zanamivir are warranted, given that the symptom-relieving and symptomatic influenza preventing effects are established and the effects on clinical complications are likely to be trivial."
Jagannath et al, 2014 (63)	"Whilst there is no evidence to either support or refute the effectiveness of NIs for treating influenza in people with CF, clinicians should continue to base their treatment decisions on clinical experience and the individual circumstances and preferences of well-informed patients."
Freemantle et al, 2014 (64)	"The studies seem to show that oseltamivir reduces mortality. However, they are based on relatively small numbers of participants, use designs that are known to be open to substantial biases, and were not optimally designed or conducted. We consider the findings interesting but inconclusive."
Ebell et al, 2013 (38)	"In summary, oseltamivir reduces the duration of symptom among patients in the ITT population by approximately 21 hours. There is no evidence that it reduces the likelihood of hospitalization or complications requiring antibiotics in the ITT or ITTI populations, and only a slight reduction in the risk of pneumonia in the ITTI population."
Hsu et al, 2012 (62)	"Our findings indicate that the use of oral oseltamivir to treat influenza may provide net benefit by reducing mortality and the duration of symptoms and complications of influenza."
Jefferson et al, 2012 (20)	"Oseltamivir shortens duration of symptoms by less than a day in people with influenza-like illness (ILI) (the intention-to-treat (ITT) population) but there is no evidence of an effect on hospitalisations."

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Appendix Table 5—**Continued**

Systematic Review	Conclusion/Recommendation
Wang et al, 2012 (60, 61)	"If near-patient testing is available and economic resources permit, oseltamivir may be considered for the treatment of children aged one to 12 years with influenza infection provided that therapy can be commenced within 48 hours of the start of the illness. However, the benefits of oseltamivir treatment are likely to be relatively modest."
Jagannath et al, 2010 (59)	"Whilst there is no evidence to either support or refute the effectiveness of NIs for treating influenza in people with CF, clinicians should continue to base their treatment decisions on clinical experience and the individual circumstances and preferences of well-informed patients."
Jefferson et al, 2010 (58)	"We do not recommend NIs for routine use in seasonal influenza except for life-threatening illness, and in circumstances where they used as an adjunct to other public health measures. We urge caution in the administration of NIs until some of the problems such as psychotropic effects and resistance have been clarified."
Jefferson et al, 2009 (39)	"Because of the moderate effectiveness of neuraminidase inhibitors, we believe they should not be used in routine control of seasonal influenza."
Shun-Shin et al, 2009 (56)	"While morbidity and mortality in the current pandemic remain low, a more conservative strategy might be considered prudent, given the limited data, side effects such as vomiting, and the potential for developing resistant strains of influenza."
Matheson et al, 2007 (47) (prophylaxis)	"At present, therefore, the evidence supporting the use of oseltamivir for the prevention, rather than treatment, of influenza in children remains weak."
Jefferson et al, 2006 (55)	"We do not see a role for the use of neuraminidase inhibitors in seasonal influenza, since the evidence shows that they are ineffective against influenza-like illness."

CF = cystic fibrosis; ILI = influenza-like illness; ITT = intention-to-treat; ITTI = intention-to-treat infected; NAI = neuraminidase inhibitor; NI = neuraminidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; SLCI = symptomatic laboratory-confirmed influenza; WHO = World Health Organization.