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Title:

Financial conflicts of interest and neuraminidase inhibitors for influenza: an analysis of systematic reviews

Authors:

Adam G. Dunn[1], Diana Arachi[1], Joel Hudgins[2,3], Guy Tsafnat[1], Enrico Coiera[1], Florence T. Bourgeois[2,3]

Affiliations:

1. Centre for Health Informatics, The University of New South Wales

2. Division of Emergency Medicine, Boston Children's Hospital

3. Department of Pediatrics, Harvard Medical School

Abstract

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 examining the use of neuraminidase inhibitors in the prophylaxis or treatment of influenza, published between January 2005 and May 2014, and employing a systematic search protocol.

Measurements: Two investigators, blinded to information identifying authors of the reviews, independently classified the presentation of evidence as favourable or not favourable to the clinical use of neuraminidase inhibitors. Financial conflicts of interest were determined for each author using the index reviews, other publications, and web-based searches. Associations between financial conflicts of interest, drug prophylaxis and treatment assessments, and presence of critical appraisals of the quality of the evidence were assessed.

Results: Twenty-six systematic reviews were identified, of which 13 examined influenza prophylaxis and 24 examined treatment, accounting for 37 distinct assessments. Among assessments associated with a financial conflict of interest, 7/8 (88%) were classified as favourable, compared with 5/29 (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 an 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.

Conclusions: Reviewers with financial conflicts of interest may be more likely to present evidence about neuraminidase inhibitors in a favourable manner and recommend these drugs for prophylaxis and treatment of influenza compared with authors without financial conflicts of interest.

Introduction

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 impact the design of trials (2), the conduct of trials (3), and the reporting of trial results (4-7). Furthermore, financial ties and industry funding appear to result in higher rates of favourable 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, 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, not only of the continuing emergence of strains with unknown drug responses, but also the increasing awareness in the medical community that, until recently, our 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 a number of key trials had not been disclosed (18, 19). As a result, systematic reviewers analysing and synthesising 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 based on 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 numeric 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 favourable 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 Cochrane Systematic Reviews Database. Searches were performed using the keywords "influenza" and "neuraminidase inhibitors", "oseltamivir", "zanamivir", "peramivir", or "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 January 1, 2005. These articles were manually reviewed to identify those that focused on the use of neuraminidase inhibitors for influenza prophylaxis or treatment (e.g. excluded articles primarily about drug development or other manufacturing processes). We selected all reviews that employed 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 performed on May 26th, 2014.

Cochrane reviews are periodically updated to incorporate new evidence and the results and conclusions 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 re-written by a subset of the authors for publication in medical journals as abridged versions in order to increase dissemination. These reports undergo separate peer review and are prepared based on a selection of the complete results. We considered these reviews separately as well, but also conducted 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 to an author's research group, and the funding of medical writers for the systematic review. These financial conflicts of interest were identified using information regarding affiliations or funding listed in the systematic reviews, as well as in any other articles published by one of the authors during the three years prior to the publication of the index systematic review. In addition, we searched authors' personal and institutional webpages, GlaxoSmithKline and Roche lists of disclosures, and performed web searches combining the names of the author, drugs, and pharmaceutical companies in order to identify any additional information about financial relationships. Details of the specific financial conflicts of interest identified for each author are listed in the appendix (Appendix Table 1).

For each systematic review, we recorded whether prophylaxis or treatment assessments were made, the forms of evidence to be included (e.g. randomized controlled trials, observational studies), the specific clinical outcomes assessed, the populations examined, and whether meta-analyses were performed. We also examined whether the reviews included information concerning the validity or quality of the primary literature. Specifically, we recorded whether there were statements addressing (a) non-publication of primary studies or publication bias, including tests performed by the reviewers to assess for bias in meta-analyses (e.g. Egger's or Begg's test (33, 34)); (b) difficulty in accessing comprehensive study data; and (c) the prevalence or role of industry in conducting and funding the primary studies.

Data Analysis

Two investigators (DA and JH) were provided with redacted copies of each review (prepared by AD) 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 acknowledgements or references. The investigators independently evaluated the reviews and classified the prophylaxis and treatment assessments as favourable or not favourable towards the use of neuraminidase inhibitors. They were instructed to perform this grading based on 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's kappa: 0.72, $P<0.001$). Disagreements were resolved by a third investigator using the same redacted copies (FB).

Descriptive analyses were conducted to examine the relationships between financial conflicts of interest and the grading of the systematic reviews. A sensitivity analysis excluding the summary reviews was performed to further examine this relationship. We also assessed the

association between financial conflicts of interest and the inclusion of statements addressing the validity or quality of the primary evidence.

Study funding

This study was funded by the Australian National Health and Medical Research Council. The funder 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 four databases using the specified search criteria, with 26 systematic reviews included in the final cohort (Figure 1). Thirteen of the reviews examined prophylaxis and 24 treatment of influenza, accounting for 37 distinct assessments (Table 1). In terms of review methods, seven were Cochrane systematic reviews and 19 conducted and reported a meta-analysis (73%). The evidence inclusion criteria were limited to randomised controlled trials for 14 of the systematic reviews (54%) and five included evidence form clinical study reports or patient level data. The main populations examined were healthy adults (18 of 26 systematic reviews), children (13/26), and hospitalised patients (6/24). 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, hospitalisation, and mortality, mostly in combination. Five of the reviews were updates of prior Cochrane reviews and three were summary reviews based on Cochrane reviews.

Association between financial conflicts of interest and favourable 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 two cases and no additional conflicts were identified based on 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 favourable. Among the assessments pertaining to prophylaxes, 23% (3/13) were favourable, while 38% (9/24) of those addressing treatment supported the use of neuraminidase inhibitors (Table 1).

Among assessments associated with a financial conflict of interest, 7/8 (88%) were graded as favourable, compared with 5/29 (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 favourable in both cases; 2/2 (100%) vs. 1/11 (9%) for prophylaxis, and 5/6 (83%) vs. 4/18 (22%) for treatment. These results did not change substantially in the sensitivity analysis excluding the summary reviews from the analysis (2/2 (100%) systematic reviews with financial conflicts of interest were graded as favourable for prophylaxis vs. 1/8 (12%) without financial conflicts of interest, and 5/6 (83%) vs. 4/15 (27%) for treatment).

Among the systematic reviews that were graded as favourable, there were three disconnected groups of authors with financial conflicts of interest and four other groups of authors that were not connected by co-authorship to systematic reviews with relevant financial conflicts of interest. Among the systematic reviews that were not graded as favourable, the majority (10/16, 62%) belonged to a single connected group of co-authors, 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. Examining the inclusion and exclusion of evidence for the subset of reviews that studied duration of symptoms using only evidence from randomised controlled trials, we found no unexplained exclusions of available primary clinical trials.

Validity and/or 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 underpinning the review (Table 2, Appendix Table 2). Reviewers without financial conflicts of interest more often included a statement about publication bias (15/19, 79%) than reviewers with financial conflicts of interest (1/7, 14%). Ten systematic reviews addressed difficulties accessing comprehensive study data and eight 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 the potential presence of bias in the synthesis and interpretation of primary evidence. We found that systematic reviews by authors with financial conflicts of interest were more likely to report favourably 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 two 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 impact 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 favourably (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 favourable 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, reporting no evidence that they reduce the risk of hospitalisation and complications, and discouraging stockpiling (Appendix Tables 3 and 4) (22, 38, 39). Factors that might 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 based on 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 a number of downstream effects to the conflicting assessments on the effectiveness of neuraminidase inhibitors. Clinically, 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. Conversely, 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 the vast majority of the primary evidence included in the systematic reviews is based on industry-sponsored clinical trials. Some have argued that industry-sponsored research should not be published in journals (45), and the recognition of a persistent bias in systematic reviews might support this stance. However, this is likely to be inefficient in an environment where most systematic reviews are out of date (46), and the individuals that 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 of the limitations of our study is that we were unable to determine which of the assessments regarding the efficacy of neuraminidase inhibitors is most accurate. It is possible that authors without financial conflicts of interest were predisposed to a less favourable view of the evidence because of existing controversies and uncertainties around the primary evidence. We were also unable to determine what factors contributed to the different conclusions between reviews written by authors with and without financial conflicts of interest. While 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.

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 favourable to the use of neuraminidase inhibitors, suggesting that industry influence may have contributed to the inconsistent conclusions. 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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Address for reprint requests:

Adam G. Dunn, PhD, Centre for Health Informatics, The University of New South Wales, Sydney, NSW 2052, Australia. Email: a.dunn@unsw.edu.au

Co-Author addresses:

Diana Arachi, Centre for Health Informatics, The University of New South Wales, Sydney, NSW 2052, Australia

Joel Hudgins, MD, Division of Emergency Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115, United States.

Guy Tsafnat, PhD, Centre for Health Informatics, The University of New South Wales, Sydney, NSW 2052, Australia

Enrico Coiera, MBBS, PhD, Centre for Health Informatics, The University of New South Wales, Sydney, NSW 2052, Australia

Florence Bourgeois, MD, MPH, Division of Emergency Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115, United States.

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Figures

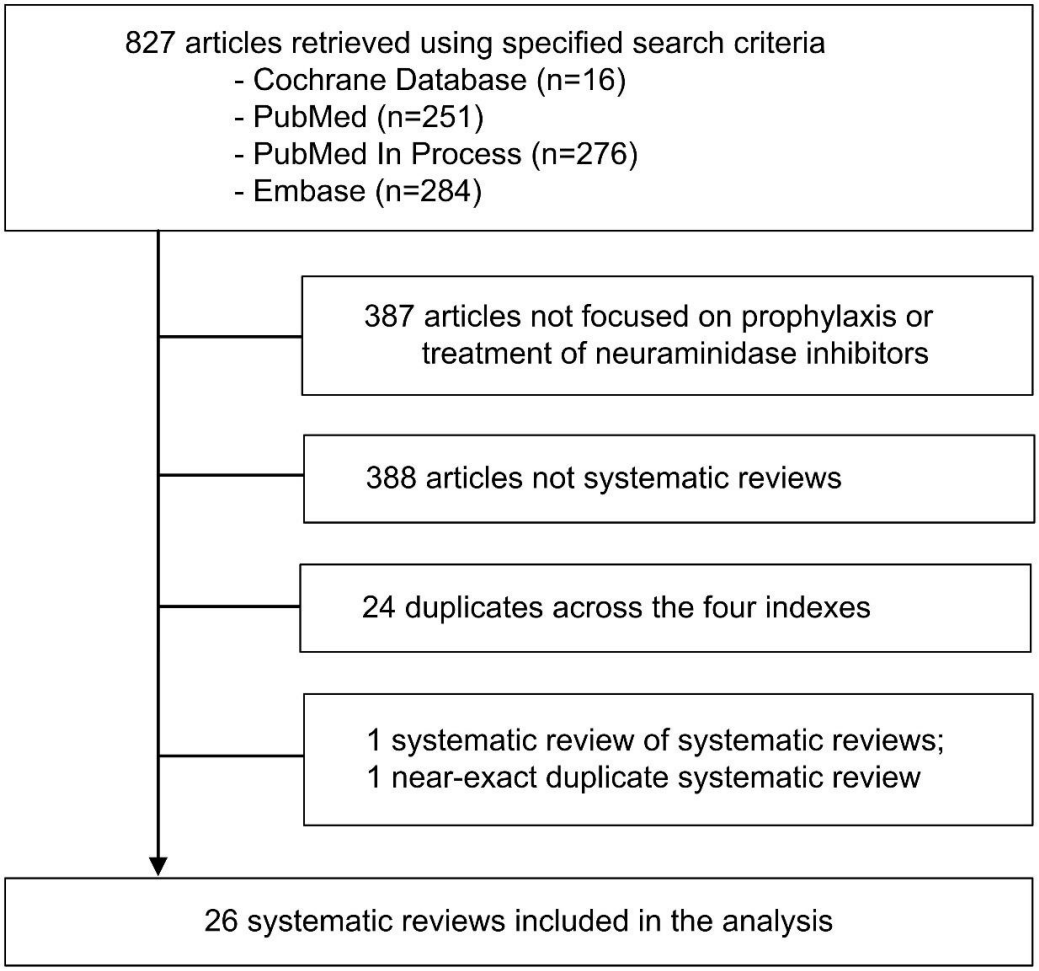

Figure 1. Eligible systematic reviews included those with outcomes related to the treatment or prophylaxis of influenza.

Table 1. Characteristics of systematic reviews examining prophylaxis and treatment outcomes for neuraminidase inhibitors

	Graded as favourable											Not graded as favourable															
	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)	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)	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)
Neuraminidase inhibitor																											
Zanamivir	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●		●		●
Oseltamivir	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●
Systematic review design																											
Cochrane systematic review	●															●	●	●	●			●				●
Includes a meta-analysis	●		●	●		●		●	●	●	●	●	●	●	●	●	[3]	●	●		●	[3]		●	●	●
Evidence inclusion																											
Published randomised controlled trials	●		●	●		●		●	●			●	●	●	●	●	●		●		●	●				
Published observational studies					●		●		●	●										●			●			
Pharmacoeconomic studies		●																								
Clinical study reports or patient-level data											●							●						●	●	●
Prophylaxis outcomes																											
Influenza-like illness	●	NA	NA		NA	NA	NA			NA	NA	●		●	NA	●	NA	●		NA	NA	NA	NA	●	●	●
Confirmed influenza	●	NA	NA	●	NA	NA	NA	●	●	NA	NA	●	●	●	NA	●	NA	●	●	NA	NA	NA	NA	●	●	●
Treatment outcomes																											
Duration of symptoms	●	●	●	NA				NA	●			●	●	●	●	●	●	●	●	●	●	●		●	●	●
Complications	●	●	●	NA		●	●	NA	●			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hospitalisation	●	●	●	NA			●	NA	●			●			●		●	●	●	●	●	●		●	●	●
Mortality			●	NA	●	●	●	NA	●	●	●									●			●			●
Patient populations																											
Healthy adults		●	●	●	●	●		●	●			●		●	●	●		●		●	●		●	●	●	●
Children	●	●			●			●	●				●					●	●	●			●	●	●	●
Hospitalised patients		●		NA	●		●	NA		●	●									●						
Other populations[1]		●	●	●	●	●	●	●	●						●		●			●		●	●			

Updates and summary reviews		
Update of prior review		● ● ● ● ●
Summary review[2]		● ● ●
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 favourable for treatment	● ● ● NA ● ● ● NA ● ● ●	
Graded as favourable for prophylaxis	NA NA ● NA NA NA ● ● NA NA	NA NA NA NA NA
Financial conflicts of interest		
Financial conflict of interest present	● ● ● ● ● ●	●

[1]Other populations include pregnant women, patients with cystic fibrosis, elderly persons, and populations with underlying conditions.

[2]Summary reviews are prepared based on reviews published in Cochrane Database of Systematic Reviews.

[3]Reviewers were unable to undertake meta-analyses because no evidence was identified.

Table 2. Consideration of validity and/or quality of primary clinical studies in systematic reviews of neuraminidase inhibitors

	Reviews without a financial conflict of interest	Reviews with a financial conflict of interest
Publication bias among clinical studies	15/19	1/7
Access to comprehensive study data	10/19	0/7
Industry support of clinical studies	8/19	0/7