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Methodological quality of systematic reviews on influenza vaccination

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Abstract

Background: There is a growing body of evidence on the risks and benefits of influenza vaccination in various target groups. Systematic reviews are of particular importance for policy decisions. However, their methodological quality can vary considerably.

Objectives: To investigate the methodological quality of systematic reviews on influenza vaccination (efficacy, effectiveness, safety) and to identify influencing factors.

Methods: A systematic literature search on systematic reviews on influenza vaccination was performed, using MEDLINE, EMBASE and three additional databases (1990-2013). Review characteristics were extracted and the methodological quality of the reviews was evaluated using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. U-test, Kruskal-Wallis test, chi-square test, and multivariable linear regression analysis were used to assess the influence of review characteristics on AMSTAR-score.

Results: Fourty-six systematic reviews fulfilled the inclusion criteria. Average methodological quality was high (median AMSTAR-score: 8), but variability was large (AMSTAR range: 0-11). Quality did not differ significantly according to vaccination target group. Cochrane reviews had higher methodological quality than non-Cochrane reviews ($p=0.001$). Detailed analysis showed that this was due to better study selection and data extraction, inclusion of unpublished studies, and better reporting of study characteristics (all $p<0.05$). In the adjusted analysis, no other factor, including industry sponsorship or journal impact factor had an influence on AMSTAR score.

Conclusions: Systematic reviews on influenza vaccination showed large differences regarding their methodological quality. Reviews conducted by the Cochrane collaboration were of higher quality than others. When using systematic reviews to guide the development of vaccination recommendations, the methodological quality of a review in addition to its content should be considered.

Keywords: influenza vaccination; systematic review; meta-analysis; quality appraisal tool; AMSTAR; methodological quality

Introduction

When considering the best available evidence regarding vaccination, results of randomized controlled trials (RCTs), systematic reviews, and meta-analyses on vaccine efficacy and safety are commonly used to guide immunization policy decisions. For influenza vaccines, however, the unique epidemiological features of influenza viruses with seasonal variations potentially leading to a mismatch between vaccine and circulating strains complicate the interpretation of single studies reporting data from only one or two seasons and increase the importance of summarized evidence in terms of systematic reviews. In addition, since most influenza vaccines are licensed only based on RCTs demonstrating immunogenicity and not efficacy in preventing clinical outcomes, there is a need to consider high-quality observational studies assessing vaccine effectiveness (1, 2). Finally, the interpretation of efficacy and effectiveness studies is further complicated by the fact that there are obvious differences in influenza vaccine efficacy/effectiveness by vaccine type and age-group (3) . Therefore, systematic reviews of high quality that address the safety and protective effects of influenza vaccination in various vaccination target groups are of particular importance.

Systematic reviews and meta-analyses are used to synthesize results of primary investigations on a specific subject and have been advocated as a way to keep up to date with current medical literature (4). Using a rigorous methodology with a clearly formulated research question and a comprehensive search strategy, systematic reviews should provide reproducible results and include all potentially relevant studies, thereby limiting bias and random errors (5, 6). When quantitative results are statistically summarized in meta-analyses they can provide more robust estimates than single studies (4, 7). However, systematic reviews and meta-analyses may differ considerably in their methodological quality (8, 9). Accordingly, systematic reviews with major methodological flaws might lead to false conclusions on the evidence, which might have a negative impact on decision-making processes (10).

Therefore, critical appraisal of the quality of systematic reviews is important. Several instruments have been developed that assess the quality of systematic reviews and meta-analyses (11-13). Based

on the most commonly used instruments, Shea et al. developed a tool for the *assessment of multiple systematic reviews* (AMSTAR) to measure their methodological quality, comprising 11 domains (14). AMSTAR can be used as a cumulative score where a higher number of fulfilled domains ("yes") corresponds to a higher methodological quality, which translates in a maximum (i.e. highest quality) score of 11 points (15, 16).

The goal of this study was to systematically identify all systematic reviews on the efficacy, effectiveness and safety of vaccines used against seasonal influenza in various target groups and to assess their methodological quality using the AMSTAR tool. Furthermore, we investigated which characteristics had an impact on the quality of these reviews.

Methods

Literature search and study selection. To identify systematic reviews on influenza vaccination we performed a systematic literature search (date of search: 15 May 2013) using MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment Database (for search strategy, see Appendix 1).

To be eligible, a systematic review had to fulfill the following inclusion criteria: 1) systematic review on the efficacy, effectiveness and/or safety of vaccines against seasonal influenza; 2) published after 1990; 3) written in English or German. Two reviewers (CR and TH) independently screened titles and abstracts of identified publications. Potentially eligible publications were reviewed as full text. Disagreements were resolved by discussions until consensus was achieved.

Data extraction and assessement of methodological quality. From each eligible systematic review, two independent reviewers (CR and TH) extracted study characteristics and assessed methodological quality. In case of disagreements, a final decision was made by consensus.

The AMSTAR tool was used to determine the methodological quality of the included systematic reviews (14). Investigators assessed each included review along the 11 domains of

AMSTAR (Box). Each domain was answered with either “yes”, “no”, “not applicable (n/a)” or “can’t answer”. AMSTAR summary score was formed by summarizing the number of domains which were answered with “yes”. A data base was constructed including the extracted review characteristics and the results of the quality assessment process for the AMSTAR summary score as well as for all 11 AMSTAR domains.

Definitions. Vaccination target groups: Each review was allocated independently by both reviewers (CR and TH) to one of the following groups according to the vaccination target groups defined in the respective review by in- and exclusion criteria: healthy children, healthy adults, elderly persons, health care personell, patients with lung diseases, patienties with malignancies, immunocompromised patients. Reviews covering healthy adults and healthy children without exclusion of special risk groups were defined as “general population”. Reviews focusing on specific vaccines (e.g. only intradermal vaccines) or covering other (e.g. multiple sclerosis) or more than one of the above mentioned subgroups (e.g. healthy and chronically ill children and adults) were defined as miscellaneous. Again, any disagreement was resolved by discussion between the authors.

Specialized journal: A journal was defined as “specialized” if its aims and scopes focuses on vaccination or infectious diseases.

Impact factor: For the purpose of this study, the Thomson Reuters Impact factor was used as of May 2013 (http://wokinfo.com/essays/impact-factor/).

Journal article version of a Cochrane review: Systematic review that has been published –in addition to the Cochrane journal- as a shortened version in a non-Cochrane journal. In addition to the main analysis which included both versions of these reviews, a sensitivity analysis was performed by excluding the full Cochrane versions of the respective systematic reviews.

Publication bias: According to the recommended use of the AMSTAR-tool, systematic reviews with less than 10 studies were scored for domain 10 “yes” if the authors mentioned that publication bias could not be assessed because of fewer than 10 included studies.

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107 *Statistical analysis*. Results of descriptive statistics were displayed as median and range or n (%), as
108 appropriate. Differences in AMSTAR summary scores according to review characteristics were
109 compared using Mann-Whitney U-test or Kruskal-Wallis test. Chi-squared test was used to compare
110 single AMSTAR domains. Multivariable linear regression was applied to analyze the influence of
111 review characteristics on AMSTAR summary score. Two-sided hypothesis tests were performed and a
112 p-value of less than 0.05 was considered as statistically significant. All calculation were made using
113 IBM SPSS Statistics 20.

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Results

The systematic literature review led to the identification of 564 publications. After exclusion of irrelevant records or studies which did not fulfill the inclusion criteria (see Appendix 2 for the list of excluded studies), a total of 46 systematic reviews (17-62) were found to be eligible (**Figure 1**). Review topics covered by the included systematic reviews are shown in **Table 1**. Two updates of systematic reviews were published after the time of the literature search and were not included in this article (63, 64).

Table 2 summarizes major characteristics of the included systematic reviews. About 50% were published in 2010 or later in a specialized journal. A quarter of them were Cochrane reviews, less than 20% of the reviews were funded by pharmaceutical companies and about 50% included observational studies. Observational studies were less likely to be included in Cochrane than in non-Cochrane reviews (3/11 (27.3%) vs. 22/35 (62.9%)) and in reviews funded by pharmaceutical industry (1/6 (16.7%) vs. 24/40 (60.0%)), respectively; however, these differences were not statistically significant (p=0.08 for both).

On average, methodological quality of the systematic reviews was high, indicated by a median AMSTAR summary score of 8, but variability was large (range: 0-11).

We then analyzed whether methodological quality of reviews differed according to review topic (i.e. vaccination target group). As shown in **Figure 2**, AMSTAR summary scores did not differ largely between review topics, except for reviews on vaccination in the general population, which tended to be of lower quality than those on other topics. However, differences in AMSTAR scores between topics were not statistically significant. Therefore, we decided to perform all subsequent analyses on the entire set of reviews as one single study base.

In the next step, we analyzed which characteristics of the reviews had an impact on methodological quality. **Table 3** shows AMSTAR summary scores according to the presence or absence of major study characteristics (bivariate analyses). Cochrane reviews had a significantly higher methodological quality than non-Cochrane reviews (p=0.001). Furthermore, reviews published

in specialized journals were of slightly but significantly lower quality than those which came from generalized journals (p=0.03). None of the other factors had an impact on methodological quality.

In order to analyze the impact of shortened "journal article versions" of Cochrane reviews, we performed a sensitivity analysis excluding the full-length Cochrane versions of the respective reviews from the database, i.e. references (23, 31, 38, 39) and repeated the main analysis. In this restricted data set, Cochrane reviews still had significantly higher AMSTAR summary scores (median: 9; range: 8-10) than non-Cochrane reviews (median: 7; range: 0-10; p=0.004), whereas the score did not differ regarding all other review characteristics (publication date; specialized journal; impact factor; no. of included studies; inclusion of observational studies; funding).

To further determine the extent by which these factors influenced the methodological quality of the systematic reviews on influenza vaccination, we performed multivariable linear regression analysis (**Table 4**). According to R^2, 27% of the variability of the methodological quality of the systematic reviews was explained by the seven factors in the model. However, in this model, only Cochrane review status (yes/no) had a significant influence on AMSTAR summary score. This result was confirmed when stepwise regression was performed to eliminate non-significant covariates: Again, Cochrane review status was the only covariate which influenced AMSTAR summary score (p=0.001; R^2=0.21). Therefore, we aimed to analyze whether these differences in review quality are caused by particular methodological features of Cochrane reviews. Accordingly, we compared the proportion of reviews which fulfilled the different AMSTAR domains (i.e., domains were answered by "yes") between Cochrane and non-Cochrane reviews (**Figure 3**). Cochrane reviews had significantly higher methodological quality (i.e., domains were more often answered by "yes") regarding domains No. 2 (duplicate study selection and data extraction), No. 4 (status of publication used as inclusion criterion) and No. 5 (list of included and excluded studies provided) (all p<0.05).

Discussion

In view of an expanding body of evidence related to the safety and protective effects of influenza vaccination and the complexity of the topic, we aimed to investigate the methodological quality of the available systematic reviews. To the best of our knowledge, this is the first study which used the AMSTAR tool to assess the quality of systematic reviews in the field of immunization in general and on influenza vaccination in particular. We found that on average systematic reviews on influenza vaccination had a high quality, with reviews conducted by the Cochrane collaboration being of higher quality than others. Although AMSTAR score was highest for reviews focusing on influenza vaccines in healthcare workers, lung diseases and malignancies with a median score of 9, and lowest in reviews dealing with the general population (median of 5), this difference was not statistically significant. The fact, that the overall quality of published systematic reviews on influenza vaccination is generally high is important for clinicians and health policy decision makers when the best available evidence is considered to guide immunization policy decisions. However, since some reviews revealed obvious flaws leading to low AMSTAR scores and one review even received an AMSTAR score of zero, critical appraisal of the methodological quality remains important in the field of systematic reviews on influenza vaccination.

So far, only one study has assessed the methodological quality of systematic reviews and meta-analyses on vaccines. Using the Oxman-Guyatt tool, Vito et al. systematically investigated the methodological quality of systematic reviews of vaccines in general and found it to be not satisfactory (65). In their paper, they identified major flaws in comprehensiveness of literature search, selection of studies for inclusion, quality assessment of included studies, and analysis of publication bias. Methodological quality of the systematic reviews was found to depend on type of included studies (RCTs vs. observational studies), year of publication, financial support (non-profit vs. for-profit support), and assessment of statistical heterogeneity. By contrast, in our study only Cochrane review status (Cochrane review vs. non-Cochrane review) had an impact on the methodological quality of reviews focusing on influenza vaccines. Differences in the quality between

Cochrane and non-Cochrane reviews were attributed to duplicate study selection, the inclusion of grey literature, and the provision of a list of excluded and included studies. However, when comparing our results with those by Vito et al. it has to be taken into account, that (i) the study of Vito and colleagues investigated the quality of reviews on all types of vaccinations (although 25 reviews on influenza vaccines were included) and (ii) the methodological quality was assessed by a different tool (66) and not the AMSTAR instrument, limiting direct comparison.

In line with our results, in other areas of medicine a higher methodological quality of Cochrane reviews was found when compared with non-Cochrane reviews. In the field of assisted reproductive technologies Windsor et al. observed that the methodological quality of Cochrane reviews was superior to non-Cochrane reviews using the AMSTAR tool (15). They identified main differences regarding the AMSTAR domains No. 1 ('a priori design'), Nr. 3 ('comprehensiveness of literature search'), Nr. 5 ('list of included and excluded studies') and Nr. 7 ('assessment of the scientific quality of included studies'). Using the 'Overview Quality Assessment Questionnaire' (OQAQ) quality assessment tool, Moseley et al. showed that conduct of systematic reviews on physiotherapy interventions according to the methodology of the Cochrane Collaboration improves review quality (67). Finally, applying the Oxman-Guyatt tool Collier et al. found that systematic reviews of the Cochrane Skin group were methodologically more rigorous than other systematic reviews in dermatology (68).

Interestingly, in our study we were unable to identify differences in methodological quality when comparing systematic reviews that were funded by pharmaceutical companies to those without such funding. In contrast, Jørgensen et al. found that industry supported reviews had more favorable conclusions and were less likely to report methodological limitations of included trials than corresponding Cochrane reviews of the same drugs (69). It is important to understand in this respect that issues like drawing conclusions or highlighting limitations are not captured by tools like AMSTAR, which are used to measure only the methodological quality of systematic reviews. Therefore, even if pharmaceutical funding did not affect the methodological quality of influenza vaccination reviews,

reporting of potential conflicts of interest and funding sources remains important when the results of systematic reviews are interpreted and conclusions are drawn.

It is furthermore important to note that according to our study, none of the included non-Cochrane reviews and less than 20% of Cochrane reviews declared conflict of interest of all included studies (AMSTAR domain 11). This is corroborated by Roseman et al. who investigated to which extend systematic reviews of drug treatments published in the *Cochrane Database of Systematic Reviews* reported conflicts of interest from included trials and the review itself. Only 30% of reviews reported information on funding source of included trials and only 20% reported information on trial funding for all included trials (70). To this end, there is a need for improvement in both, Cochrane and non-Cochrane reviews in reporting potential conflicts of interest for all included studies and the review itself.

According to AMSTAR domain 10, publication bias was reported in only 36.4% of Cochrane and 40% of non-Cochrane reviews. Publication bias can occur when studies on the same research question are more likely to be published when containing statistically significant or “hoped-for” results (71). Since undetected publication bias may lead to imprecise or misleading results of systematic reviews, statistical approaches such as funnel plots and regression test proposed by Egger and colleagues has been developed and should be used to detect publication bias (72). However, even if measures to identify publication bias have improved in recent years (73), the reporting rate in reviews on influenza vaccines is still not satisfactory. It should be emphasised, that the purpose of this paper was not to analyze or discuss results of included reviews and that even reviews of high methodological quality should be interpreted with caution. For example, even “empty reviews” that did not identify any study to be eligible can reach a high AMSTAR-score if performed thoroughly. And for certain research questions a review based solely on RCTs might provide only limited evidence, irrespective of its methodological quality. In such cases, inclusion of observational studies might increase the overall value of the review, but this does not necessarily translate to a higher methodological quality as indicated by a higher AMSTAR score. Thereby, AMSTAR score, as a

measure of methodological quality, does not provide information on the usefulness of the results of the respective systematic review for the development of prevention policies.

It is possible, that differences in the average AMSTAR-scores may be partly explained by the fact, that Cochrane authors could publish their articles in an online journal with unlimited space, whereas non-Cochrane authors publish in other journals with limitation of word numbers. However, the sensitivity analysis revealed, that the impact of unlimited space of Cochrane journals was small in regard of the methodological quality. Moreover, since most AMSTAR-items (except item 5) could be answered by a single sentence and almost all journals offer the opportunity to upload online supplementary material as standard practice, these issues can be easily met also by authors of standard journal articles. In general, methodological flaws in the conduct of systematic reviews could be avoided by consulting references such as the Cochrane handbook before starting a systematic review.

Our study has several strengths: It is based on a a systematic literature search strategy, thereby ensuring comprehensiveness. Furthermore, the AMSTAR tool was applied to systematic reviews on vaccination which covered a variety of vaccination target groups. However, our approach was limited to English and German language papers and to those published after 1990, which were chosen for the reason of practicability.

In summary, this methodological study shows that systematic reviews on influenza vaccination had on average a high methodological quality but variability was large. Reviews conducted by the Cochrane collaboration were of higher quality than others, whereas other factors such as industry sponsorship, journal impact factor, and type of included studies did not significantly influence the methodological quality of systematic reviews on this topic. Our findings support the notion that a high methodological quality is the basic precondition of systematic reviews for identifying the best available evidence regarding specific research questions. However, a high methodological quality does not automatically reflect usefulness of the content of a review. To this

269 end, both methodological quality of a review and its content have to be considered when using

270 systematic reviews to guide immunization policy decisions.

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Tables

Table 1: Topics of included systematic reviews on influenza vaccination

Topic (vaccination target groups)	**N (reviews)**
General population	3
Healthy children	8
Healthy adults	3
Elderly persons	4
Health care workers[1]	5
Patients with lung diseases[2]	5
Immunocompromized patients[3]	4
Patients with malignancies	2
Miscellaneous	12

[1] also includes studies on indirect benefits for other groups, e.g. patients managed by health care personnel

[2] incl. studies on patients with COPD, asthma, cystic fibrosis and bronchiectasis

[3] also includes studies on patients with HIV

Table 2: Characteristics of included systematic reviews

Characteristics of reviews (n=46)	**Median (range) or n (%)**
Year of publication	2010 (1995-2013)
Specialised journal	26 (57)
Impact factor	3.5 (0-39)
Cochrane review	11 (24)
No. of pages	11.5 (5-227)
- without Cochrane reviews	10 (5-74)
No. of included studies	13 (0-209)
Observational studies included	25 (54)
Funding by pharmaceutical company	6 (13)
AMSTAR score	8 (0-11)

Table 3: AMSTAR summary scores according to characteristics of systematic reviews

Characteristics of reviews	**Yes**[1]	**No**[1]	**p-value**[2]
Publication after 2007[3]	8 (2-11)	7 (0-10)	0.29
Specialised journal	7 (0-10)	8 (5-11)	**0.03**
Impact factor $\geq$ 3.5[4]	8 (4-11)	7 (0-10)	0.20
Cochrane review	9 (8-11)	7 (0-10)	**0.001**
No. of included studies $\geq$ 13[4]	7 (3-11)	8 (0-10)	0.25
Observational studies included	8 (0-11)	8 (2-10)	0.55
Funding by pharmaceutical company	6 (2-9)	8 (0-11)	0.38

[1] Median (range)

[2] Mann-Whitney U-Test

[3] AMSTAR was published first in 2007

[4] median of all included journals/studies

Table 4: Multivariable linear regression analysis: AMSTAR summary score according to characteristics of systematic reviews (R^2=0.27)

Characteristics in the model	Beta	T	p-value
Publication year after 2007[1]	-0.006	-0.03	0.97
Specialised journal	-0.055	-0.28	0.78
Impact factor $\geq$ 3.5[2]	-0.19	-1.03	0.31
Cochrane review	0.58	2.40	**0.02**
No of included studies $\geq$ 13[2]	0.08	0.53	0.60
Observational studies included	0.11	0.69	0.50
Funding by pharmaceutical company	-0.17	-1.07	0.29

[1] AMSTAR was published first in 2007

[2] median of all included journals/studies

Box: Description of AMSTAR domains (according to (14))

1. Was an ‘a priori’ design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusion?
9. Were the methods used to combine the findings of the studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Were potential conflicts of interest declared?

Figure legends

Figure 1: Selection process for systematic review of systematic reviews on influenza vaccination.

Figure 2: AMSTAR scores according to vaccination target groups of systematic reviews. Data are medians and ranges. AMSTAR scores do not differ significantly between target groups (p=0.08; Kruskal-Wallis test). HCW: health care workers.

Figure 3: Individual AMSTAR scores for each domain (1-11) given as percentage of reviews receiving a "Yes" in Cochrane reviews (n=11) vs. non-Cochrane reviews (n=35). Groups are significantly different for domains 2, 4 and 5 ($p<0.05$; chi-squared test). For description of AMSTAR domains 1-11, see Box.

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Appendix 1

Search strategy for the systematic review

#1 “influenza”

#2 “vaccin*”

#3 “immuniz*”

#4 “meta-analysis”

#5 “systematic review”

#6 “#2 OR #3”

#7 “#4 OR #5”

#8 “#1 AND #6 AND #7”

(restrictions: publication year 1990 – 2013; language: English, German; Species: Human)

Appendix 2

List of excluded studies:

(i) Duplicates (n=29)

(ii) Not a systematic review (n=12): (1), (2), (3), (4), (5), (6), (7), (8), (9) Erratum, (10), (11), (12)

(iii) Update of a (Cochrane) review (n=7): (13), (14), (15), (16), (17), (18), (19)

(iv) Systematic review of systematic reviews (n=2): (20), (21)

(v) Language other than English or German (n=2): (22) (23)

(vi) No data on influenza vaccine efficacy, effectiveness or safety (n=2): (24), (25)

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Figures

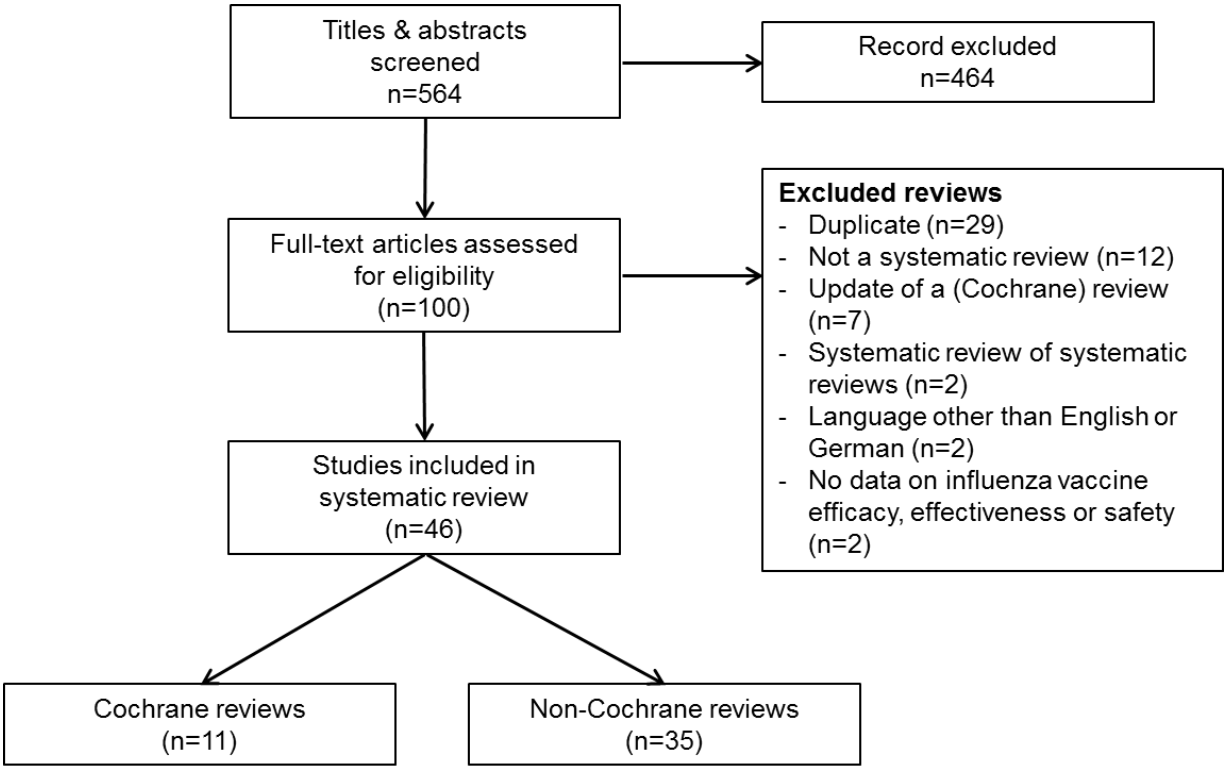

Figure 1: Selection process for systematic review of systematic reviews on influenza vaccination.

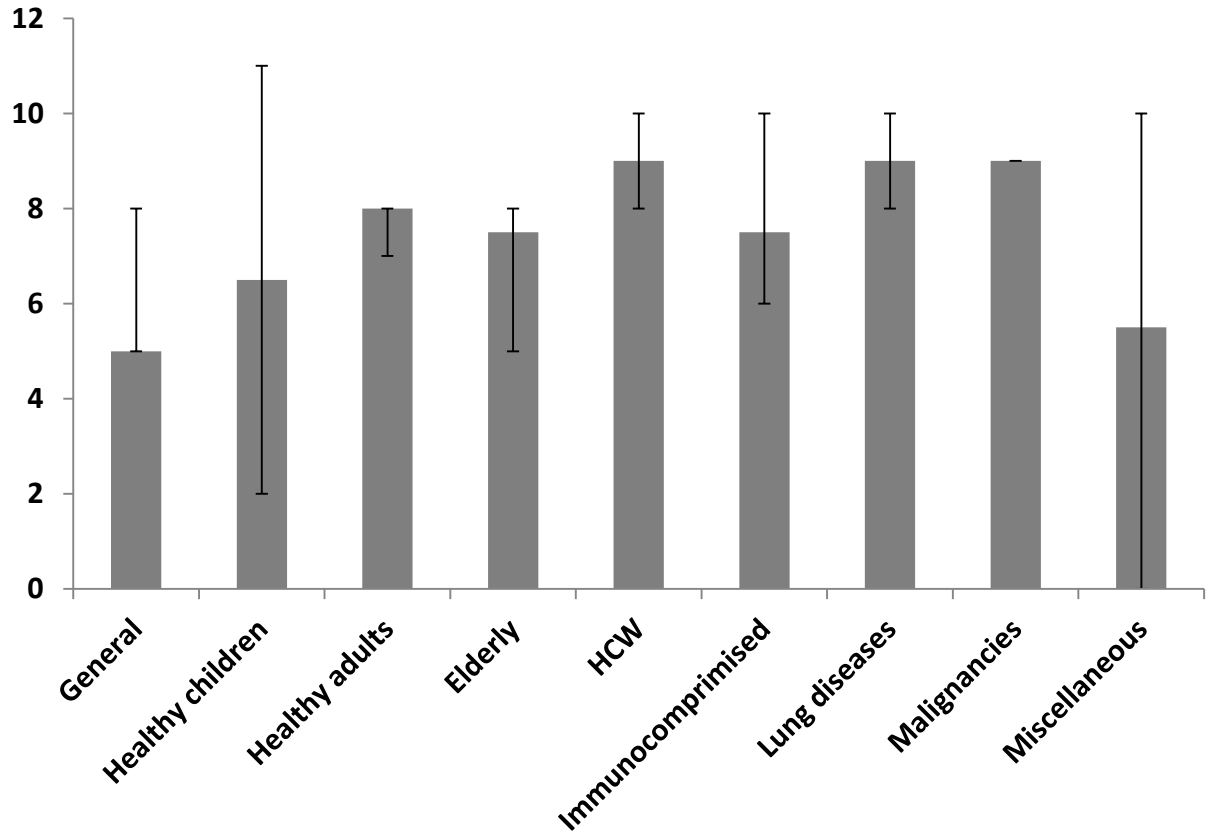

Figure 2: AMSTAR scores according to topics of systematic reviews. Data are medians and ranges. AMSTAR scores do not differ significantly between topics (p=0.08; Kruskal-Wallis test).

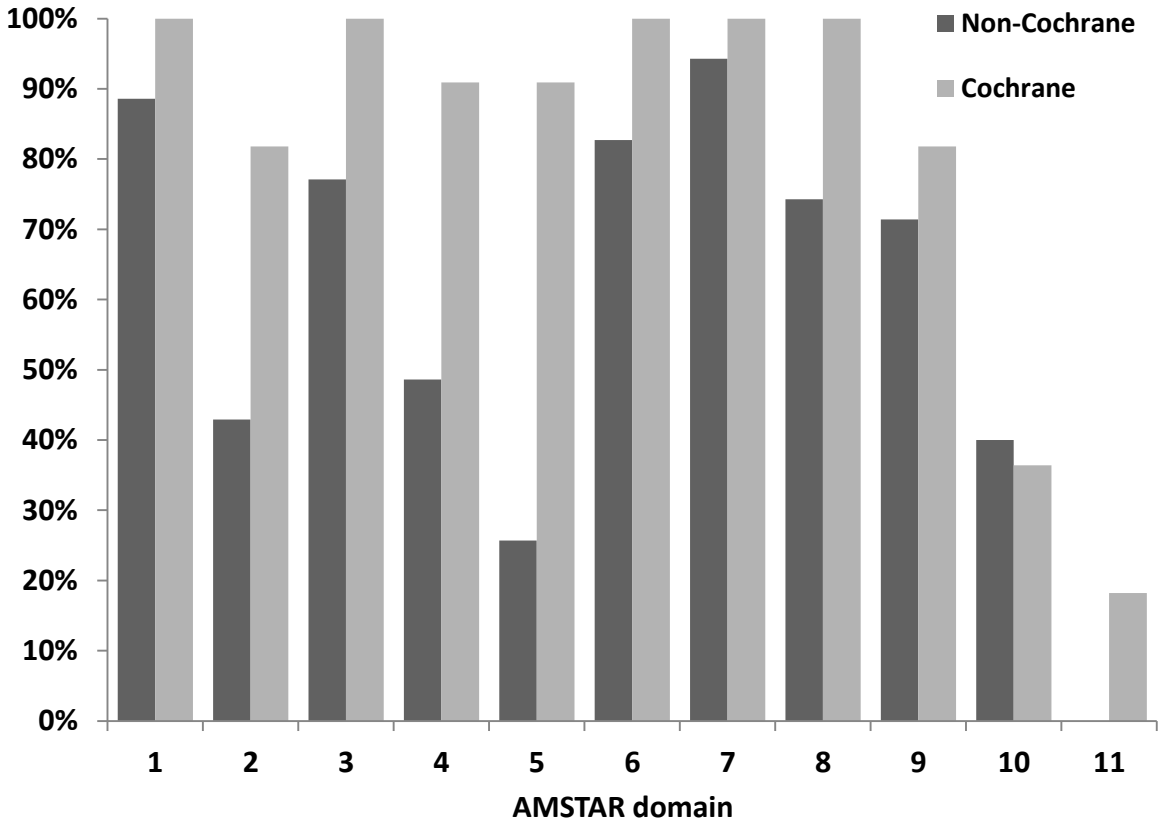

Figure 3: Proportion of reported AMSTAR domains (items 1-11) in Cochrane vs. Non-Cochrane reviews. Groups are significantly different for items 2, 4 and 5 ($p<0.05$; chi-squared test).