Format for ANSWERING REVIEWERS

January 9, 2015

Dear Editor,

Please find enclosed the edited manuscript in word format (file name: 12894-Review.docx).

Title: Effectiveness of 7-valent pneumococcal conjugate vaccine: a meta-analysis of post-marketing studies

Author: Chiara de Waure, Maria Lucia Specchia, Silvio Capizzi, Mufida Aljicevic, Milos Dujovic, Admir Malaj, Walter Ricciardi

Name of Journal: *World Journal of Meta-Analysis*

ESPS Manuscript NO: 12894

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer:

Reviewer 1
This is a well-written meta-analysis. The major question is whether it is timely.
Answer: Thank you for the warning. We are aware that PCV7 has been replaced by PCV13. Notwithstanding, because of the recent introduction of PCV13, important amount of data are available only for PCV7. This has been already stated in the introduction but, following your comments, we have reported that some early evidence is being produced on PCV13 also but that they are too early in order to be meta-analyzed.

Minor comment: 1. How does your meta-analysis add to the one from Pavia and colleagues?
Answer: Thank you for the warning. In discussion we have already addressed Pavia and colleagues meta-analysis but we have specified that the added value of our review was to provide data on real world efficacy. In order to make it clear, a sentence specifying the importance of the study of effectiveness of health interventions has been included.

Major comments:
1. In the discussion make it clear that: Efficacy trials (explanatory trials) determine whether an intervention produces the expected result under ideal circumstances. Effectiveness trials (pragmatic trials) measure the degree of beneficial effect under "real world" clinical settings (see http://www.ncbi.nlm.nih.gov/books/NBK44024/.).
Answer: Thank you for the suggestion. We have expanded on the concept in the discussion and we have included two new references.

2. Two conjugate vaccines are available since 2009, one 13-valent (PCV13) the other 10-valent (PCV10). The first pneumococcal conjugate vaccine, a 7-valent product, is no longer in use. Given that all recipients of PCV 7 will soon be older than 5 years, how relevant is your meta-analysis in 2014?
Answer: Thank you for the warning. We are aware that PCV7 has been replaced by PCV13. Anyway,

because of its recent introduction (from 2010 onward), very few studies dealing with the effectiveness of PCV13 are available. With this respect the assessment of PCV7 effectiveness may be useful in order to foresee PCV13 overall impact under real conditions. This justifies our interest in PCV7 effectiveness. A sentence has been included in introduction in order to make this concept clear.

3. A post-licensure assessment of serotype-specific PCV13 effectiveness exists (see: The Lancet Infectious Diseases. Volume 14, Issue 9, September 2014, Pages 839–846). PCV13 vaccine effectiveness after two doses before age 12 months or one dose from 12 months was 75% (95% CI 58–84). Vaccine effectiveness was 90% (34–98) for the PCV7 serotypes and 73% (55–84) for the six additional serotypes included in PCV13. This reference should be discussed and cited. Again, the reader is forced to wonder, how relevant is your meta-analysis in 2014?
Answer: Thank you for the warning. We have included the paper by Andrews et al. in both introduction and discussion. Furthermore we have included other references on PCV13 effectiveness and we have reported results released by population-based studies already published.

Reviewer 2
The authors performed an interesting meta-analysis on a highly relevant topic. However, there is one minor concern, which needs to be addressed prior to a possible publication:
1. Please revise your work according to the PRISMA statement published by the CONSORT group.
Answer: Thank you for the warning. The paper has been revised according to PRISMA statement even though the most of items were already taken into consideration in the original version. With this respect, PRISMA checklist has been filled in and is underneath. In particular, in the amended version, the following points were further elaborated on: the objective, the selection process, the data extraction, the assessment of risk of bias across studies and the relevance of results for key groups. Please note that the reported pages are referred to the clean version of the amended paper.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Meta-Analysis*

Sincerely yours,

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Section/topic	No	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Review protocol does not exist
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	The assessment of risk of bias was not performed
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Additional analyses were not performed
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 and figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	The assessment of risk of bias was not performed
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8 and figures 4 and 5

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Additional analyses were not performed
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	The work was not funded