PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union
AUTHORS	Shields, Gemma; Elvidge, Jamie; Davies, Linda

VERSION 1 - REVIEW

REVIEWER	Rebekah Pennington NICE, UK
REVIEW RETURNED	27-Oct-2016

GENERAL COMMENTS	I understand that the paper present a systematic review of economic evaluations of 'flu vaccination of elderly patients in Europe. There is a lot of context provided in the intro which is helpful, but I think that this could be condensed to focus on the specific aim of this paper, The search strategy, review process, and PRISMA look good. However, the interventions and comparators vary between the studies making it difficult to draw meaningful conclusions as to whether 'vaccination' is cost-effective - suggest it would be necessary to restrict to only studies that compare 'vaccination' to 'no vaccination' for this analysis. Herd immunity effects mean that the incremental effectiveness of increasing vaccination levels is not linear (for example increasing from 80% to 90% is different from increasing from 10% to 20%). Therefore the coverage level before and after the intervention should be extracted for each study. At that point it may only be appropriate to compare results between studies with similar before and after coverage levels. You may also need to exclude studies which considered other populations - and clarify if you are looking for studies which consider exclusively elderly populations, or report results for elderly patient vaccination strategies. Synthesizing results across economic evaluations is always difficult and is noted in published literature - it may not be appropriate to try and generalise from these studies. It may be more interesting to focus on explaining differences in the results of the different studies - this has been started could be expanded. Jit et al 2013 (ref 44) may be a useful starting point. The discussion about model types, and the comparison to EEACTs is interesting. The paper contains a lot of information and would benefit from a clearer focus. I don't think it is feasible to draw broad conclusions about the cost-effectiveness of flu vaccination for the elderly, and instead recommend that the paper focuses on exploring the

	differences between results from different studies. If the models are simple, consider rebuilding one and testing the different inputs to understand what is driving the results. I fully support the conclusion that future economic evaluations should follow good practice guidelines. But I am unclear how RCTs could be ethically conducted to allow EEACTs when flu vaccinations are known to be effective and are recommended by policy? It may be worth noting the work of Baguelin et al (2013 and 2015) who have built a complex epidemiological model for flu vaccination in England and Wales.

REVIEWER	Mathieu Uhart Sanofi Pasteur MSD, France
REVIEW RETURNED	28-Oct-2016

GENERAL COMMENTS	The manuscript is a review of the evidence of the economic evaluation of seasonal vaccination for the elderly population in EU union. It is clear and well written. The methodology is well described and results are correctly presented. Unfortunately, the discussion and conclusion are not balanced and do not reflect the results of the review. Indeed, the aim of the study is double: - to determine whether flu vaccination has been demonstrated to be cost effective in the elderly population and at the view of the results the answer seems positive (7 studies conclude it is cost-effective or cost-saving versus no intervention; 1 study conducted in the low risk population concludes it is not). - to review the strength of the evidence based and here lookng at the table "summary of critical appraisal", it seems the main limitation is related to the lack of robust data related to vaccine efficacy in 65+. The distinction between these two aspects must be presented more clearly. The discussion and conclusion must be revised highlights what can be conclude from the literature, what are the limitations and what could be done. The abstract conclusion must be updated accordingly. Major comments: - in the introduction, a presentation of the different type of vaccines (trivalent or quadrivalent at least) is missing. It is also important to explain what is a mismatch (topic which is broached later in the manuscript). -p16 line 30: please add in the summary tables a column presenting the SA run for each study. If all studies run 4 sensitivity and only the vaccine price is missing i do not think we can say the conclusion of the analysis is not robust. -p16 line 35: the statement "this is not a robust conclusion" is too assertive. I would suggest to tell robustness of the conclusion is questionable. Since all SA show positive results we cannot say with certainty that the results is false. - Discussion: The discussion focus only on the lack of robustness of the study but does not develop at all what can be drawn from these studies. Your primary objective was to determine whether flu vaccinaiton in the elderly has been demonstrated as cost effective.

	We do not have the answer. Yet, your review show that 90% of the studies concluded it is cost effective, all (or most?) of the SA had positive results. One study had contradictory results but evaluated cost-effectiveness in "low risk" elderly population. I think this should be discussed more in detail. Overall, i do not have the feeling the discussion reflects what is found in the literature. Minor comments: p4 Line 7-10: the sentence is unclear: effectiveness to reduce flu burden or associated compmlication? Are you sure we do not have data on this ? p4 Line 18: mathcing must be defined. p4 Line 16: the 23% effectiveness relates to the elderly living in long term care facilities. It is a sub population not representative to the entire elderly population. It is discussed by the author in its article "The conclusions drawn from studies done in individuals who live in long-term care facilities are different to those drawn from studies in individuals"who live in the community". This precision must be specified as such or the sentence deleted. p10 line 24: I do not understand why the vaccination rate can be different from 0% in the non intervention arm ? p14 line28-29: this should be reflected in your conclusions p15 line 41: it would be interesting to discuss the impact of herd immunity on the cost effectiveness. In this study, what was the impact of herd immunity detailed? p15 line 48: Here you present cost of service redesign as an important parameter that must be taken into account to correctly evaluate efficiency of flu vaccination. It is not that straightforward. Indeed, this aspect is more related to the increase of the VCR, i.e. to the evolution of program itself than to the vaccination. Besides, since most model were static ones, the VCR had no impact on the ICER. Overall, it is questionnable to include the cost of clinic opening in the economic evaluation of flu vaccination. I think the the statement "is likely to be highly relevant" should be softened +++. p17 line18: Why widening the searches to the grey literature or unpublished reports may have been more likely to identify studies with inconclusive or negative CE results? This should be referenced. One may also imagine studies found in grey literature are of poor quality/less robust ? p17 line33: it is quite surprising you conclusion opens on the value of complex modelling techniques in order have a more accurate assessment of the benefit of vaccination. Indeed, what come out of the manuscript is that existing cost effectiveness evaluation are not robust because of the quality of data essentially. Use of more complex models means more parameters and more sources of uncertainty. If we are not able to get robust data for a simple model it is unlikely the use of more complex model will help us to get a more robust evaluation of the efficiency.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

"There is a lot of context provided in the intro which is helpful, but I think that this could be condensed to focus on the specific aim of this paper."

Author reponse: Thank you for this suggestion. We have shortened the introduction to focus on the issues around policy decisions to target older people for influenza vaccination.

"However, the interventions and comparators vary between the studies making it difficult to draw meaningful conclusions as to whether 'vaccination' is cost-effective - suggest it would be necessary to restrict to only studies that compare 'vaccination' to 'no vaccination' for this analysis."

Author reponse: Thank you for identifying this issue. We have reordered Table 1-3 to clearly separate studies comparing vaccination types from those comparing a formal vaccination strategy to no vaccination strategy (e.g. implement targeted vaccination versus no targeted vaccination). We have revised and re-ordered the results section to follow these categorisations. We have kept studies that compare vaccination types in the paper as we think these will still be relevant to different audiences, however our changes make the differences in the papers clearly.

"Herd immunity effects mean that the incremental effectiveness of increasing vaccination levels is not linear (for example increasing from 80% to 90% is different from increasing from 10% to 20%). Therefore the coverage level before and after the intervention should be extracted for each study. At that point it may only be appropriate to compare results between studies with similar before and after coverage levels."

Author response: This is a really interesting point. As only one study considered the impact of herd immunity we have discussed this separately and added a note explaining the issue. This is likely to be an important issue for future researchers as more complex modelling techniques are starting to be used and are likely to incorporate herd immunity. We have added the following text to the results: The inclusion of herd immunity has important implications for the vaccination coverage in the intervention and comparator arm. Herd immunity means that the impact of increasing vaccination levels is not linear, e.g. an equal change in the coverage rate between studies could have very different results depending on what the comparator/usual care coverage rate is, as the scope for benefits from herd immunity will be different. Whilst this does not affect this review because only one study included herd immunity, it is an important point for future researchers looking to compare study results as more studies including herd immunity become available in the future.

"You may also need to exclude studies which considered other populations - and clarify if you are looking for studies which consider exclusively elderly populations, or report results for elderly patient vaccination strategies."

Author response: We have focused the article, in particular the introduction, to make it clearer that we are focusing solely on the elderly population and only included studies that reported results for elderly patient vaccination strategies alone or separate to other populations. We have added the following text to the methods to clarify: Studies did not need to exclusively look at this age group, but had to present the results for the elderly population separately to other populations if they did consider wider populations.

"Synthesizing results across economic evaluations is always difficult and is noted in published literature - it may not be appropriate to try and generalise from these studies. It may be more interesting to focus on explaining differences in the results of the different studies - this has been started could be expanded. Jit et al 2013 (ref 44) may be a useful starting point. The discussion about model types, and the comparison to EEACTs is interesting."

Author response: As noted by the reviewer, broad conclusions are challenging and we have gone further to investigate the differences between studies which helps to highlight this point. In addition, we have added a little more detail on the findings on the Jit paper in relation to RCT based evaluations.

"The paper contains a lot of information and would benefit from a clearer focus. I don't think it is feasible to draw broad conclusions about the cost-effectiveness of flu vaccination for the elderly, and instead recommend that the paper focuses on exploring the differences between results from different

studies. If the models are simple, consider rebuilding one and testing the different inputs to understand what is driving the results."
Author response: Many thanks for your comment. As noted in the responses above we have focused the paper more by differentiating between studies comparing types of vaccines and those comparing vaccination versus no intervention. We have revised the paper to report and explore possible differences between study results in more detail. We agree that rebuilding one of the models would be interesting but feel that this is outside the scope of this literature review. As we note in the critical appraisal and discussion, there are gaps in the data and results reported in the papers, making it difficult to reproduce one or more of the studies.
"I fully support the conclusion that future economic evaluations should follow good practice guidelines. But I am unclear how RCTs could be ethically conducted to allow EEACTs when flu vaccinations are known to be effective and are recommended by policy?"
Author response: We have adjusted this recommendation to also include a prospective study (as many elderly people choose not to undergo vaccination). We feel that the lack of clinical evidence about the effectiveness of vaccines in the elderly population means that further prospective controlled studies (including RCT's and observational cohort studies) would add valuable information to the evidence base. We have edited the text to clarify this point:

Economic evaluations integrated into long-term, prospective, controlled studies (e.g. observational cohort studies or RCTs) or prospective study in elderly populations would help to address the evidence gaps around effectiveness, service use and health benefit. Since the influenza virus mutates each season and differences in vaccine matching each season, a combination of multiple studies and those conducted over several influenza seasons are needed. Improvements in the evidence base would support the development and analysis of more sophisticated modelling techniques. Such models could then characterise the epidemiology of influenza and complications in elderly people, incorporate the impact of herd immunity within the elderly population and between age groups. Robust data about service use and health benefits would allow more detailed estimates of the potential for different vaccination strategies for older people to be cost effective in different settings.
"It may be worth noting the work of Baguelin et al (2013 and 2015) who have built a complex epidemiological model for flu vaccination in England and Wales."
Author response: Thank you for suggesting these references. We have added to the text: The body of economic evidence suggest that influenza vaccination of elderly populations may be cost effective, but data, methodological transparency and exploration of uncertainty are lacking. Baguelin et al developed a complex epidemiological model to explore the relative cost effectiveness of vaccination in different low and high risk groups. Whilst these evaluations give an indication of the value of complex models, both studies also faced limitations in data about the effectiveness of vaccines and estimates of service use and health benefits.

Reviewer 2
"Unfortunately, the discussion and conclusion are not balanced and do not reflect the results of the review. Indeed, the aim of the study is double:
- to determine whether flu vaccination has been demonstrated to be cost effective in the elderly population and at the view of the results the answer seems positive (7 studies conclude it is cost-effective or cost-saving versus no intervention; 1 study conducted in the low risk population concludes it is not).
- to review the strength of the evidence based and here lookng at the table "summary of critical appraisal", it seems the main limitation is related to the lack of robust data related to vaccine efficacy in 65+.
The distinction between these two aspects must be presented more clearly. The discussion and conclusion must be revised highlights what can be conclude from the literature, what are the limitations and what could be done.
The abstract conclusion must be updated accordingly. "

Author response: Thank you for your helpful suggestions. We have made the following changes to address these:
• The study aims now read: This study had two aims. Firstly, to determine whether influenza vaccination interventions were demonstrated to be cost-effective in older people in the EU The second aim was to critically appraise the methods and data to evaluate the validity and robustness of the study findings, to inform policy makers and future research.
• As noted in the responses to reviewer 1, we have restructured the results sections and added more detail to draw out the differences between studies that may influence the results.
• We have summarised the results of the studies at the start of the discussion: The majority (7/8) of the identified studies found influenza vaccination to be cost effective in an elderly European population. The studies indicated some differences what vaccination strategy may be cost-effective. Adjuvant or quadrivalent vaccinations had more favourable results compared to standard vaccinations Vaccination targeted to high risk groups of older people were generally more cost-effective and passive vaccination strategies appeared more cost-effective than opportunistic strategies. Decision makers using this evidence would need to check which papers are most relevant to their research question. Most scenarios tested in sensitivity analysis still resulted in favourable cost-effectiveness results for influenza vaccination. In addition, the studies that conducted probabilistic sensitivity analysis concluded that the likelihood of cost-effectiveness given parameter uncertainty was high. Results were sensitive to variations in the strain of influenza incidence, vaccination type, efficacy and strategy, population risk and modelling characteristics. Review findings are in alignment with the previous review identified.
• We have added sub-headings to separate out the limitations of the studies included in the review and limitations of the review
• We have revised the limitations section to provide more details about the key issues that limit the validity and robustness of the findings.
• As noted in the response to reviewer 1 we have revised the section about the implications for future research, which also helps draw out the limitations of the studies reviewed.
• The abstract conclusion has been revised to read: Conclusions: Most studies suggest that vaccination is cost-effective (7/8 studies identified at least one cost-effective scenario). All but one study used economic models to synthesise data from different sources. The results are uncertain due to the methods used and the relevance and robustness of the data used. Sensitivity analysis to explore these aspects was limited. . Integrated, controlled prospective clinical and economic evaluations and surveillance data are needed to improve the evidence base. This would allow more advanced modelling techniques to characterise the epidemiology of influenza more accurately and improve the robustness of cost-effectiveness estimates.
"- in the introduction, a presentation of the different type of vaccines (trivalent or quadrivalent at least) is missing. It is also important to explain what is a mismatch (topic which is broached later in the manuscript)."
Author response:We have added some brief text on vaccine types into the introduction: Two types are available; trivalent which protects against three viruses, and quadrivalent which protects against four viruses. Vaccines can also contain squalene-based adjuvants (e.g. MF59) which aim to improve the efficacy of vaccines. Matching has been defined in the introduction: the degree of similarity between the circulating virus and strain in the vaccine.
"-p16 line 30: please add in the summary tables a column presenting the SA run for each study. If all studies run 4 sensitivity and only the vaccine price is missing i do not think we can say the conclusion of the analysis is not robust."
Author response: We have added a summary table of the sensitivity analyses into the supplementary material. In addition, the critical appraisal section has been expanded to more fully discuss the limitations of the sensitivity analysis conducted by the studies: Most scenarios tested in sensitivity analysis still resulted in favourable cost-effectiveness results for influenza vaccination. However, there were limitations to the range of sensitivity analyses reported, given that many of the studies recognised there are issues with the evidence base. Methods used to analyse uncertainty were

varied, such that results are not comparable. The WHO recommend that sensitivity analyses for economic evaluations of vaccines should vary the following 5 parameters as a minimum: discount rates, vaccine efficacy, influenza incidence, influenza complication rates and vaccine price. None of the studies identified varied all of the recommended parameters and because of this, we cannot fully assess the robustness of the results. One of the studies performed a comprehensive one-way sensitivity analysis; presenting a resulting tornado diagram. One study did not perform any one-way/scenario analysis. The remaining studies chose to vary a limited selection of key variables, but did not explain the rationale for these. Three studies provided and justified ranges used in sensitivity analyses. The remainder detailed the ranges but did not provide justification, which means that validity cannot be assessed. Three studies included probabilistic sensitivity analysis, but one did not report the results restricted to the elderly populations alone. This lack of thorough investigation and transparency restricts our ability to assess the robustness of the results or to explore the transferability of study results to alternative countries, settings and influenza seasons.
"-p16 line 35: the statement "this is not a robust conclusion" is too assertive. I would suggest to tell robustness of the conclusion is questionable. Since all SA show positive results we cannot say with certainty that the results is false."
Author response: As noted in the response above we have revised the critical appraisal section and removed this statement.
"- Discussion: The discussion focus only on the lack of robustness of the study but does not develop at all what can be drawn from these studies. Your primary objective was to determine whether flu vaccinaiton in the elderly has been demonstrated as cost effective. We do not have the answer. Yet, your review show that 90% of the studies concluded it is cost effective, all (or most?) of the SA had positive results. One study had contradictory results but evaluated cost-effectiveness in "low risk" elderly population. I think this should be discussed more in detail. Overall, i do not have the feeling the discussion reflects what is found in the literature. "
Author response: As noted in the response to reviewer 1 we have revised the Discussion, which now includes a clear summary of the reported results of the studies included. We have added to the discussion about the limitations of the studies reviewed to draw out the implications for the robustness of the results.
"p4 Line 7-10: the sentence is unclear: effectiveness to reduce flu burden or associated compmlication? Are you sure we do not have data on this ?"
Author response: We have added text to clarify this as well as an additional more recent reference (a good quality systematic review).
"p4 Line 18: mathcing must be defined."
Author response: A short definition has been added in brackets (noted in a previous comment).
"p4 Line 16: the 23% effectiveness relates to the elderly living in long term care facilities. It is a sub population not representative to the entire elderly population. It is discussed by the author in its article "The conclusions drawn from studies done in individuals who live in long-term care facilities are different to those drawn from studies in individuals"who live in the community". This precision must be specified as such or the sentence deleted."
Author response: Thank you for spotting this. The text has been revised to reflect this and a brief overview of the study findings in the elderly population living in the community has been added for clarity. We have revised the text to read: When focusing specifically on the elderly population effectiveness appears to be much lower; with an estimate of 23% efficacy for elderly individuals living in care homes in seasons where vaccine matching (the degree of similarity between the circulating virus and strain in the vaccine) is good. For individuals living in the community the same study noted that vaccines were not statistically significantly effective at preventing influenza, although well matched vaccines provided benefits in reducing related admissions to hospital and pneumonia.
"p10 line 24: I do not understand why the vaccination rate can be different from 0% in the non intervention arm ?"
Author response: Coverage rates for intervention and comparator arms have been added into Table 1 and there is additional information discussing coverage rates in the results and critical appraisal

section. We feel that it is appropriate that the comparator/no intervention arm of most studies included a proportion of the population receiving vaccination and the intervention looks at higher levels of vaccination, as decision makers in the EU are looking to increase vaccination rates.
"p14 line28-29: this should be reflected in your conclusions"
Author response: This comment referred to the point that the majority of tested scenarios still demonstrated vaccination to be cost effective. We recognise and have made it clearer in the conclusions. In addition, we have gone into further detail about why more information is needed to increase the certainty we have about these results (e.g. studies should justify the selection of ranges and parameters for sensitivity analysis).
"p15 line 41: it would be interesting to discuss the impact of herd immunity on the cost effectiveness. In this study, what was the impact of herd immunity detailed?"
Author response: This is covered in the results section where it reads: One model included transmission rates and captured externalities arising from herd immunity... We have added some additional information on how the results changed (from being a cost-effective ICER result to being dominant) to highlight this point.
"p15 line 48: Here you present cost of service redesign as an important parameter that must be taken into account to correctly evaluate efficiency of flu vaccination. It is not that straightforward. Indeed, this aspect is more related to the increase of the VCR, i.e. to the evolution of program itself than to the vaccination. Besides, since most model were static ones, the VCR had no impact on the ICER. Overall, it is questionnable to include the cost of clinic opening in the economic evaluation of flu vaccination. I think the the statement "is likely to be highly relevant" should be softened +++."
Author response: We agree that this is a complex issue and have revised this section to read: No studies considered the cost of service redesign to increase vaccination (e.g. opening additional clinics) which may be relevant for healthcare systems with restraints on resources available (e.g. in the case of an aging population). Thus, the true cost of vaccination is likely to be underestimated across studies depending on the healthcare setting and design.
"p17 line18: Why widening the searches to the grey literature or unpublished reports may have been more likely to identify studies with inconclusive or negative CE results? This should be referenced. One may also imagine studies found in grey literature are of poor quality/less robust ?"
Author response: We have added a reference to support the statement that published economic evaluations are likely to contain favourable ICERs. We agree with the reviewer that studies identified from the grey literature may be of lower quality (e.g. less likely to follow reporting guidelines) however we don’t have any references to support this.
"p17 line33: it is quite surprising you conclusion opens on the value of complex modelling techniques in order have a more accurate assessment of the benefit of vaccination. Indeed, what come out of the manuscript is that existing cost effectiveness evaluation are not robust because of the quality of data essentially. Use of more complex models means more parameters and more sources of uncertainty. If we are not able to get robust data for a simple model it is unlikely the use of more complex model will help us to get a more robust evaluation of the efficiency."
Author response: The review firstly discusses the parameter limitation and then makes it clear that when this information is available more complex methods should be used. We have revised the discussion section with the inclusion of headers to make this flow clearer. The conclusion in the abstract has also been revised for clarity on this point.

Thanks again for taking the time to review and consider our paper