PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of targeting all elderly persons in England & Wales for yearly influenza vaccination: excess mortality due to pneumonia or influenza and time trend study
AUTHORS	Mann, Andrea; mangtani, punam; Russell, Colin; Whittaker, John

VERSION 1 - REVIEW

REVIEWER	Chris Robertson Professor Department of Mathematics and Statistics Strathclyde University 26 Richmond Street Glasgow G1 1XH I have no competing interests with respect to this work
REVIEW RETURNED	05-Mar-2013

RESULTS & CONCLUSIONS	I think that there may be a problem with the analysis of Figures 1 and 2 which I expect can be clarified. More details are in my comments
GENERAL COMMENTS	This is an important topic and one which is topical at present. The paper is extremely well written and very comprehensive. The literature review in the introduction is good and well balanced. The analysis approach will answer the main aims of the paper. I think that the modelling is well done for the most part though I have a number of queries which will mostly be for clarification. With this type of analysis you always have to make decisions and there are many that can be made at each stage. I think that the authors have made reasonable choices here – they are not necessarily the ones that I would have made but they are valid. The results are well presented and the discussion of the results is balanced. I think that the main point the authors need to address is the use of linear regression based upon a normal distribution for the excess deaths which may not be valid. Comments P6: The use of Pneumonia and Influenza Deaths together is fine though this excludes the possible effects of influenza on other respiratory cardiac deaths though these are less specific. This could be discussed. P7: It is not exactly clear how the data were adjusted. I appreciate

	that an adjustment needs to be done. Did the model contain terms for ICD changes and were these additive or did they modify the trend? Were the deaths themselves adjusted. The supplementary material has mention of dummy variables for artefacts which looks like an additive change within the model P8: Excess mortality was the sum of observed minus predicted deaths in weeks when laboratory data breached their epidemic threshold, by influenza year What is the threshold level used. I wonder if this definition of excess mortality is too stringent as it means that there is no excess mortality if there is no influenza epidemic according to a threshold criterion. If the threshold is 20% positivity for example then positivity could run at 15% for 8 weeks in one year and there be no epidemic yet go to 25% for 2 weeks in another year and lead to a potential excess. With the definition you have there are a lot of years with no excess yet there is still influenza circulating. I now see from the supplementary material that you used the upper 95% CI of the predicted count, but the principle is the same. I would have looked at different definitions of the period to calculate the excess as part of a sensitivity analysis. P8: The spline trend was investigated visually for changes of slope associated with vaccination. I think that there is a testable hypothesis of a change in slope post 2000. It might not be so easy to test this with a spline trend though would be with a piecewise linear approximation. P9: Were the age group specific models of excess mortality fitted using a normal distribution linear regression model? It is not clear from the text. The supplementary material mentions negative binomial regression for the weekly lab counts and weekly mortality data but nothing for the excess deaths in a year. If it is linear regression I don't think that this is correct as the normal assumption cannot be correct. Mostly the dummy variables are just to split into 2 groups so you could use a non parametric test as it is difficult to get a good model for excess deaths when so many years have zero. Page 10, Figure 1 and Table 1: The modelling in Fig 1 concerns me as it looks as if you are fitting a linear regression to data that are not suitable. In terms of the main purpose of the paper I would have been tempted to split the time period into 3 (no vaccination, targeted, and universal) and see if the excess deaths varied among these three groups with the primary hypothesis being the comparison of targeted with universal; this could be done with a kruskall wallis test. I think you could argue that the trend modelling you already do on weekly deaths and weekly lab counts takes into account the trend and that there is no residual trend in excess deaths. The vaccine uptake does not change all that much that a trend model is necessary. If it is necessary to have a trend then I suggest fitting a piecewise linear trend with change points at the time vaccination policy

	changed and then test for changes in the slope. I would use log(excess+1) or square root (excess) to get a better fit to a symmetric distribution. P11, Fig 2: The Confidence intervals here are symmetric and look to be based upon a normal distribution. I would be surprised it this is valid for excess deaths. Also as the main aim is to detect an effect of going from a risk based to a universal vaccination policy in those aged over 65 the periods to compare are 1989-99 against 2000-2004. I think that this is what is done but was a bit confused as there are data from 1975 onwards in table 1 and fig 1 P11: The trends described in baseline mortality are consistent with the changes to the vaccination policy. Were the knot points for the splines chosen by the authors or were default ones chosen. As there are prior hypotheses about the earliest times the changes in trends can take place there is an argument for specifying the knot points. P12: The principal findings are well elucidated.

REVIEWER	Niroshan Siriwardena, Professor of Primary and Prehospital Health Care, University of Lincoln, UK.
REVIEW RETURNED	12-Mar-2013

THE STUDY	This is a carefully designed and well argued study. One concern I have with the study is the authors' focus on excess mortality ascribed to influenza and pneumonia. They use this outcome because of its specificity. However, as the authors state in their discussion, this misses deaths due to other respiratory causes and the considerable proportion (up to a third) of influenza-related deaths from cardiovascular disease (myocardial infarction and stroke).[1] Therefore it would be better to express their main outcome more specifically as "excess mortality due to influenza and pneumonia" in the title and abstract. I would advise the paper be reviewed by a statistician who is expert in time series methods. 1. Schanzer Vaccine 2008 26:4697–4703
RESULTS & CONCLUSIONS	As argued above it would be better to express the main outcome as "excess mortality due to influenza and pneumonia" in the title and abstract.

REVIEWER	Dr Jim McMenamin Consultant Epidemiologist Respiratory Team Health Protection Scotland NHS National Services Scotland 4th Floor Meridian Court 5 Cadogan Street

	Glasgow G2 6QE
REVIEW RETURNED	18-Mar-2013

RESULTS & CONCLUSIONS	The title and objective require to be amended since the analysis is limited to consideration of the endpoints of pneumonia and influenza respectively. Subject to this change the results answer the research question.
GENERAL COMMENTS	1. This is a well conducted study into the impact of the annual influenza vaccination programme examining the impact in terms of excess mortality across the first five seasons of the routine offer of vaccine to all patients over the age of 65. The title and the objective should however be amended to reflect that this is a restricted analysis using these end points. I would suggest that the title becomes "The impact....excess mortality for pneumonia or influenza and time trend study". The Article Summary & Age objective should similarly be adjusted to accomodate this. 2. The limited years of observation of the potnetial impact of the routine vaccination programme create a difficulty. The authors rightly point out that the clinical impact of influenza in the seasons that followed 1999/2000 had a relatively low impact in terms of clinical illness complications (perhaps with the exception of Fujian virus in 2003/4 especially in chidren). The model presented provides an annual estimate of impact. One way of overcoming this is to additionally consider an average of excess deaths over the course of the seasons with central, upper and lower estimates. I would suggest this would be useful perhaps as a table for the various age groups. 3. Page 9. I would be interested to know a little more about the temperature variable chosen and the decision around location of this (I think from the table included that this was Central England and monthly). Was this monthly for convenience? Why not weekly? 4. In terms of future research tying analysis like this to annual serological studies to compare serological attack rate data for influenza across age groups would be a useful step that could overcome some of the limitations. I would encourage then authors to liaise with HPA CfI colleagues to enable this for future since I understand that a funding stream is in place for such ongoing serological studies. 5. There are by implication serious communication issues for the journal and authors to deal with since the last thing anyone wants is to threaten the current seasonal influenza vaccination programme. I am sure that editorially he journal should address this. 6. Given this important communication issue a further area of research is whether the observations can be repeated over a more recent timeframe - period during which we observed a pandemic (2009/10) a more severe flu season dominated by H1N1pdm09 virus (2010/11) and increasing vaccine uptake towards a ceiling of 75% uptake.

VERSION 1 – AUTHOR RESPONSE

Responses to reviewers' comments
Prof Chris Robertson 1 P6: The use of Pneumonia and Influenza Deaths together is fine though this excludes the possible effects of influenza on other respiratory cardiac deaths though these are less specific. This could be discussed.
Response: We feel that the wording in the Discussion (para 2) is sufficient on this point and wonder if

the reviewer might agree upon re-reading the relevant sentence: "Analysing underlying P&I of course means our estimates of excess mortality underestimate the burden of mortality due to all respiratory disease (which includes bronchitis), cardiovascular disease and other causes of death which may be linked to influenza. (19, 20) However, it was not the aim of this work to estimate the total mortality burden due to influenza. "

Prof Chris Robertson 2 P7: It is not exactly clear how the data were adjusted. I appreciate that an adjustment needs to be done. Did the model contain terms for ICD changes and were these additive or did they modify the trend? Were the deaths themselves adjusted. The supplementary material has mention of dummy variables for artefacts which looks like an additive change within the model

Response: We thank the reviewer for highlighting that our description of how the time series of weekly deaths was adjusted for artefacts was unclear: deaths themselves were adjusted (they were multiplied by correction factors estimated in a separate analysis). We have amended the first sentence of Methods para 2 to clarify this. The supplementary material makes mention of adjusting laboratory data for artefacts. This was done by including dummy variables in the models themselves.

Prof Chris Robertson 3 P8: Excess mortality was the sum of observed minus predicted deaths in weeks when laboratory data breached their epidemic threshold, by influenza year. What is the threshold level used. I wonder if this definition of excess mortality is too stringent as it means that there is no excess mortality if there is no influenza epidemic according to a threshold criterion. If the threshold is 20% positivity for example then positivity could run at 15% for 8 weeks in one year and there be no epidemic yet go to 25% for 2 weeks in another year and lead to a potential excess. With the definition you have there are a lot of years with no excess yet there is still influenza circulating. I now see from the supplementary material that you used the upper 95% CI of the predicted count, but the principle is the same. I would have looked at different definitions of the period to calculate the excess as part of a sensitivity analysis.

Response: In addition to the estimates of excess mortality we included in the paper, we also estimated excess using Serfling-like regression. The Serfling-like approach makes no use of laboratory data to inform the timing of epidemics, but simply excludes a portion of high counts when estimating baseline mortality. We excluded between 1 and 25% of high counts in a sensitivity analysis. Our conclusions were unaffected by estimating excess this alternative way. We excluded this sensitivity analysis from the paper so that the paper would not be overlong.

Prof Chris Robertson 4 P8: The spline trend was investigated visually for changes of slope associated with vaccination. I think that there is a testable hypothesis of a change in slope post 2000. It might not be so easy to test this with a spline trend though would be with a piecewise linear approximation.

Response: We thank the reviewer for suggesting the approach to testing for a change in slope of the baseline trend post-2000. We have not done this because our feeling is that the coefficient would be confounded by time-varying covariates which we are only able to speculate about and not adjust for. We have added mention of the reviewer's suggestion to Discussion para 2, with this explanation as to why we did not carry out this additional analysis.

Prof Chris Robertson 5 P9: Were the age group specific models of excess mortality fitted using a normal distribution linear regression model? It is not clear from the text. The supplementary material mentions negative binomial regression for the weekly lab counts and weekly mortality data but nothing for the excess deaths in a year. If it is linear regression I don’t think that this is correct as the normal assumption cannot be correct. Mostly the dummy variables are just to split into 2 groups so you could use a non parametric test as it is difficult to get a good model for excess deaths when so many years have zero.

Response: We thank the reviewer for correcting us and we agree linear regression is not appropriate here. We reran the analysis having transformed excess deaths using the log(excess + 1) transformation suggested by the reviewer, which resulted in residuals which are normally distributed. The same conclusions can be drawn as from the linear regression. We have amended the relevant areas in methods (para 7) and results (para 3), and have redrawn figure 2 with back-transformed coefficients from the amended analysis.

Prof Chris Robertson 6 Page 10, Figure 1 and Table 1: The modelling in Fig 1 concerns me as it looks

as if you are fitting a linear regression to data that are not suitable. In terms of the main purpose of the paper I would have been tempted to split the time period into 3 (no vaccination, targeted, and universal) and see if the excess deaths varied among these three groups with the primary hypothesis being the comparison of targeted with universal; this could be done with a kruskall wallis test. I think you could argue that the trend modelling you already do on weekly deaths and weekly lab counts takes into account the trend and that there is no residual trend in excess deaths. The vaccine uptake does not change all that much that a trend model is necessary. If it is necessary to have a trend then I suggest fitting a piecewise linear trend with change points at the time vaccination policy changed and then test for changes in the slope. I would use log(excess+1) or square root (excess) to get a better fit to a symmetric distribution.
Response: Figure 1 is intended to be descriptive only and we overlayed the linear line of best fit to help readers visualise trend. We agree with the reviewer that a linear model is not correct so we have removed the line.
Prof Chris Robertson 7 P11, Fig 2: The Confidence intervals here are symmetric and look to be based upon a normal distribution. I would be surprised it this is valid for excess deaths. Also as the main aim is to detect an effect of going from a risk based to a universal vaccination policy in those aged over 65 the periods to compare are 1989-99 against 2000-2004. I think that this is what is done but was a bit confused as there are data from 1975 onwards in table 1 and fig 1
Response: Yes, we had used linear regression which we agree was not correct (see response to point 5 above). We re-ran the regression, having transformed excess deaths using the log(excess + 1) transformation. We have redrawn Figure 2 which now shows back-transformed coefficients from this revised analysis.
Prof Chris Robertson 8 P11: The trends described in baseline mortality are consistent with the changes to the vaccination policy. Were the knot points for the splines chosen by the authors or were default ones chosen. As there are prior hypotheses about the earliest times the changes in trends can take place there is an argument for specifying the knot points.
Response: Because we were attempting first to describe the baseline trend and second to superimpose the timing of the policy change, we used default knot points (where the number of knot points required in order to satisfactorily describe the trend was chosen in a model selection exercise). We have clarified in the supplementary methods (section "Estimating excess and baseline mortality") that knot-positions were the default ones.
Prof Chris Robertson 9 P12: The principal findings are well elucidated.
Response: n/a
Prof A. Niroshan Siriwardena 10 This is a carefully designed and well argued study. One concern I have with the study is the authors' focus on excess mortality ascribed to influenza and pneumonia. They use this outcome because of its specificity. However, as the authors state in their discussion, this misses deaths due to other respiratory causes and the considerable proportion (up to a third) of influenza-related deaths from cardiovascular disease (myocardial infarction and stroke).[1] Therefore it would be better to express their main outcome more specifically as "excess mortality due to influenza and pneumonia" in the title and abstract.
Response: We thank the reviewer and agree that the title and abstract should make clear we calculated excess mortality due to pneumonia and influenza. We have amended the title, the abstract's objective, and the introduction (final sentence of first paragraph).
Dr Jim McMenamin 11 1. This is a well conducted study into the impact of the annual influenza vaccination programme examining the impact in terms of excess mortality across the first five seasons of the routine offer of vaccine to all patients over the age of 65. The title and the objective should however be amended to reflect that this is a restricted analysis using these end points. I would suggest that the title becomes "The impact....excess mortality for pneumonia or influenza and time trend study". The Article Summary & Age objective should similarly be adjusted to accomodate this.
Response: We thank the reviewer and we have made the suggested amendments (see point 10 above, as well as Article Summary, 2nd bullet).
Dr Jim McMenamin 12 2. The limited years of observation of the potnetial impact of the routine

vaccination programme create a difficulty. The authors rightly point out that the clinical impact of influenza in the seasons that followed 1999/2000 had a relatively low impact in terms of clinical illness complications (perhaps with the exception of Fujian virus in 2003/4 especially in chidren). The model presented provides an annual estimate of impact. One way of overcoming this is to additionally consider an average of excess deaths over the course of the seasons with central, upper and lower estimates. I would suggest this would be useful perhaps as a table for the various age groups.
Response: We thank the reviewer for suggesting this useful addition to the paper. We have added a supplementary figure (2) and refer to this figure in Results para 2.
Dr Jim McMenamin 13 3. Page 9. I would be interested to know a little more about the temperature variable chosen and the decision around location of this (I think from the table included that this was Central England and monthly). Was this monthly for convenience? Why not weekly?
Response: The temperature variable used was the lowest (monthly) temperature observed in a given influenza season. In the analysis of the effect of the policy change on excess mortality, the unit of observation was an influenza season, so all variables (including temperature) were collapsed to units of per influenza season.
Dr Jim McMenamin 14 4. In terms of future research tying analysis like this to annual serological studies to compare serological attack rate data for influenza across age groups would be a useful step that could overcome some of the limitations. I would encourage then authors to liaise with HPA CfI colleagues to enable this for future since I understand that a funding stream is in place for such ongoing serological studies.
Response: We thank the reviewer for this helpful suggestion and have added mention of it to the final paragraph of the Discussion.
Dr Jim McMenamin 15 5. There are by implication serious communication issues for the journal and authors to deal with since the last thing anyone wants is to threaten the current seasonal influenza vaccination programme. I am sure that editorially he journal should address this.
Response: n/a
Dr Jim McMenamin 16 6. Given this important communication issue a further area of research is whether the observations can be repeated over a more recent timeframe - period during which we observed a pandemic (2009/10) a more severe flu season dominated by H1N1pdm09 virus (2010/11) and increasing vaccine uptake towards a ceiling of 75% uptake.
Response: We thank the reviewer for this suggestion. We have revised a sentence in the final paragraph of the Discussion to include these specific points.

VERSION 2 – REVIEW

REVIEWER	Chris Robertson Professor of Public Health Epidemiology Department of Mathematics and Statistics University of Strathclyde. Livingstone Tower
REVIEW RETURNED	15-May-2013

GENERAL COMMENTS	The authors have dealt satisfactorily;y with all of my previous comments and I have no furthre comments to make