BMJ - Decision on Manuscript ID BMJ.2015.027974

Body: 10-Sep-2015

Dear Dr. Ludvigsson

Manuscript ID BMJ.2015.027974 entitled "Maternal vaccination against H1N1 influenza and offspring mortality – population based cohort study and sibling design"

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

https://mc.manuscriptcentral.com/bmj?URL_MASK=9353868dc7ab4b3e8e24449748a9399f

Yours sincerely

Georg Roeggla
groggla@bmj.com

Manuscript meeting 10.09.2015

Wim Weber (chair), Rafael Perera (stats), Elizabeth Loder, Georg Röggla, Alison Tonks, Jose Merino, Tiago Villanueva

Decision: Provisional acceptance

The committee was interested in the topic of your research. The following concerns were mentioned:

• What does the sibling analysis add?
• How much does your paper add to a recent metaanalysis on this research question (BJOG. 2015 Jan;122(1):17-26)?
• Isn't this primarily of historical interest?
• Did any of the unvaccinated women get pandemic flu?
• From a statistical point of view we would like to know more about the second comparison (within families). In particular the order of the pregnancies. If this was random or always the "index" was later than the "control". The flow chart could have some extra information about the pregnancies (with and without vaccinations) added. Mostly it is extra data needed for clarity but the analysis seems adequate.

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available below. Please also respond to the additional comments by the committee.

Reviewer(s)' Comments to Authors:

Reviewer: 1

Recommendation:

Comments:
This manuscript describes a prospective cohort study in seven healthcare regions of Sweden that assessed the risk of offspring mortality (stillbirth, early neonatal period, late infant) following exposure in utero to AS03-adjuvanted H1N1 influenza vaccine. Comparison groups included pregnant women not exposed to the vaccine in the same calendar period and non-exposed siblings to infants prenatally exposed to vaccination. Fetal death and early infant mortality following immunization with the H1N1 influenza vaccine are important vaccine safety issues which have not been completely addressed, especially the latter one. Although there was evidence already showing no association of stillbirths and H1N1 influenza vaccination, the findings in this study are re-assuring. Few studies had looked at the association of vaccination with early neonatal mortality and this study provides important evidence that supports the safety of the H1N1 influenza vaccine in this regard. The manuscript is well written, and well organized. The methodology and the design are adequate and sound. I would recommend its publication in the BMJ.

I do have some comments regarding some of the wording used by the authors in the introduction

In lines 20-25 under "With few exceptions (e.g.,increased risk of preterm birth[24] and non-significant increased risk of stillbirth[11]), research suggests that H1N1 vaccination has few adverse effects on pregnancy outcomes"
This sentence seem to imply that preterm birth and stillbirth are real risks following influenza vaccination in

pregnancy. The study the authors cite for preterm birth did find an increased relative risk but it was one finding inconsistent with most other studies. The other mention of non-significant increased risk of still birth should be taken out. The sentence should be changed. It could be changed to something like: "Most research suggests that H1N1 vaccination has few adverse effects on pregnancy outcomes"

Also in the introduction, in lines 46-55, the authors state: "Maternal vaccinations could potentially influence offspring mortality through several mechanisms. Offspring mortality could increase if fetal reactions to viral or non-viral components of the vaccine [26] have long-term consequences, or through an excess of congenital malformations as indicated by some research [21]". These statements are very speculative. The references provided (21 and 26) don't really provide solid reasons to back-up these statements.

Table 1: under the variable status at end of follow-up, what is dead referring to? Later death? Please specify

For the characteristic gestational age, mean (SD), is the number in parentheses the standard deviation or the proportion of vaccinated or not vaccinated? Please provide the gestational age in weeks

The flowchart is also explained well in the text so it could be deleted

Additional Questions:
Please enter your name: Pedro Moro

Job Title: Epidemiologist

Institution: Centers for Disease Control and Prevention

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
General comments
This is a well written paper using excellent population based data from Sweden, a reliable and original design, state of the art and novel methodological approaches, and sound and cautious interpretation. The study adds important new and relevant knowledge to the field. The study results suggest that maternal H1N1 vaccination during any trimester of pregnancy has no adverse effect on offspring mortality, during pregnancy, in the early neonatal period or in early childhood. I strongly recommend publication of this paper in BMJ, and the paper can be published as it is after minor editorial revision.

Originality - does the work add enough to what is already in the published literature? If so, what does it add?

This is a highly original study due to the combination of nearly complete population data from seven Swedish health regions (about 61% of the population in Sweden), a sibling design, and analyses of longterm mortality in offspring. The study shows no (or neutral) effect of AS03-adjuvanted H1N1 vaccination during pregnancy on offspring mortality, divided according to stillbirth, death on days 0-6 (early neonatal period) and death from day 7 until 4.6 years of age.

In their brief statement on what is already known on this topic, the authors say that "Several studies have reported a neutral relationship between maternal H1N1 vaccination during pregnancy and risk of adverse fetal outcome, but data on longterm mortality in offspring are missing." and that "Lack of adjustment for residual confounding (genetic and environmental) shared within families is a potential source for bias in earlier studies."
This study adds data on longterm mortality in offspring as well as analyses adjusted for possible residual confounding due to genetic and early environmental factors shared within families. The data required for such analyses are scarce or non-existent, and/or difficult to obtain in most countries.

This work adds the following main results:

1. H1N1 vaccination during pregnancy does not seem to influence offspring mortality after the neonatal period. This is a new finding with significant public health relevance.
2. A neutral association between H1N1 vaccination during pregnancy and adverse fetal outcome, also when intrafamilial factors are taken into account, is confirmed.

Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it?
The pandemic influenza and the different national policies for preventing and managing the risk of serious influenza disease are of great interest for the general public across the world. It is relevant for preparedness and health system governance, for policy makers, health workers, patient organizations and media. A general journal is clearly the right place for publication of this paper.

Scientific reliability
• This study is highly scientifically reliable.
• The research questions are clearly defined and appropriately answered. The primary objective of this population-based cohort study was to explore mortality in offspring of mothers undergoing influenza A(H1N1)pdm09 vaccination. A secondary objective was to examine stillbirth, early neonatal death, and offspring mortality after taking familial factors into account. This is exactly what the study does.
• The overall design is clearly adequate. In addition, the sibling design is a novel approach. This is described in the paper as follows: Cox regression was used to estimate HRs for stillbirth, early neonatal mortality (days 0-6) and subsequent mortality (beginning on day 7) in vaccinated vs. non-vaccinated women with fetal/infant age as the study time scale, adjusting for mother's age at birth, BMI, parity, smoking, country of birth, disposable income, and sex of offspring. According to the authors, there was no evidence of nonproportional hazards. In addition, they examined risks of stillbirth, early neonatal death, and offspring mortality according to trimester of vaccination. For the analysis of stillbirth, the exposure (vaccine during pregnancy or during the trimesters) was time-dependent. They began follow-up at 22 gestational weeks. Thus, if the mother were vaccinated before the start of follow-up, the fetus was considered exposed from the start; otherwise, the subject was considered unexposed until the date of vaccination.
Sibling comparisons were performed to take familial factors into account when comparing exposed and unexposed individuals. From the Medical Birth Register, the authors identified all siblings of infants prenatally exposed to the mothers' vaccinations during pregnancy. They were therefore able to compare offspring mortality between children with the same mother according to vaccination exposure.
• The participants are adequately described. The study links data from several routine sources (the Swedish Medical Birth register, the Swedish Cause of Death Register, vaccination data from Swedish counties and Statistics Sweden). The participants are transparently described in the paper, in a flow chart (Figure 1) and in Table 1 (page 22).
• The methods are adequately described and the reporting complies with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) standard for reporting of cohort studies. A checklist of items according to STROBE is included as supplementary material.
• The results answer the research question. They are credible, well presented and easy to grasp.
• Interpretation and conclusions are warranted by and sufficiently derived from the data. The authors are aware of the main weaknesses of the study and discuss these ("Among the weaknesses is our lack of data on miscarriage before gestational week 22, and consequently we were unable to study whether this may have influenced the lack of association between H1N1 vaccination and stillbirth. Neither did we have data on factors influencing the decision to vaccinate during pregnancy and we cannot rule out that residual confounding influenced our results")
• The message is clear and relevant for a general reader.
• The references are up to date, relevant, and as far as I am informed they are complete with no glaring omissions.
• The abstract, summary and key messages communicate the study efficiently and reflect accurately what the paper says.

Minor specific comments

• Page 3, line 32-33 Data sharing. Why do the authors say that "No additional data will be made available"? What does this mean? I thought that linked Swedish routine registry data were available for any research group provided that one has ethical approval and purposes within the legal framework for such data. What happens if other researchers want to challenge the analyses in this study? Can they apply for access to the linked data prepared for this study?
• Page 3, line 9. I believe that it should be written "source of bias" rather than "source for bias".
• Page 8, line 47. I assume it is correct that only siblings discordant for both exposure and outcome contributed to the analyses but I (and probably other readers) need this to be explained in some more detail. Why is it not only discordance for exposure which is required?
• Page 10, line 50. Should it be "If the mother was…" rather than "If the mother were.."?

Additional Questions:
Please enter your name: Camilla Stoltenberg

Job Title: Director general, Professor

Institution: Norwegian institute of public health

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: Yes

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: - The Norwegian iinstitute of public health is a governmental organisation which purchases and distributes vaccines in Norway on behalf of the Norwegian government. Funding is provided annually in the national budget and approved by the parliament.
- The Norwegian institute of public health applies for and is a recipient of competive funding from public and private research funding agencies such as the Research Council of Norway, EU, NIH, The Welcome Trust, The Oak Foundation and others.

Reviewer: 3

Recommendation:

Comments:
The study appears well constructed and clearly reported, and will provide useful information to women considering vaccination during pregnancy. I am, however, unsure of how the sibling control works for a study that includes perinatal death as an outcome measure, particularly as risk of stillbirth is increased in women >35 and then again in those >40. Could the authors add a few more sentences describing how the sibling control group adds reassurance to the study design?

Additional Questions:
Please enter your name: Laura Price

Job Title: Research and Information Officer

Institution: Sands, the stillbirth and neonatal death charity

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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If you have any competing interests (please see BMJ policy) please declare them here: The study appears well constructed and clearly reported, and will provide useful information to women considering vaccination during pregnancy.

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d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis"

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the

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Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

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• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

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• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
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For a study of a diagnostic test:
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• PPV and NPV (positive and negative predictive values)

For a systematic review and/or meta-analysis:
point estimates and confidence intervals for the main results

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were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

Date Sent: 10-Sep-2015