Author's response to reviews

Title: The effect of influenza vaccination among general practitioners: a controlled trial [NCT00221676].

Authors:

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Version: 2 Date: 26 April 2006

Author's response to reviews: see over
Dear editor,

Thank you for giving us the opportunity to revise our article RE: 1099046454923839 - The effect of influenza vaccination among general practitioners: a controlled trial [NCT00221676].

We are very grateful for the comments and suggestions of the reviewers through which we could clarify and refine the article. We copied these remarks below, answered each comment separately in italic and adjusted our article accordingly. The text is also corrected for the use of the English language by International Science Editing, http://www.internationalscienceediting.com. Through this editing the title slightly changed in “The effect of giving influenza vaccination to general practitioners: a controlled trial [NCT00221676]”

In the main time, reference 16 changed from ‘in press’ to an exact reference:


We hope you will reconsider the revised manuscript for publication. If there is any indistinctness left, we are willing to clarify or to give more precise answers where necessary.

Yours sincerely,

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Detailed responses on the reviewers' remarks

Version: 1 Date: 13 March 2006
Reviewer: Eelko Hak
Reviewer's report:
This study is an addition to the recently published study on the efficacy of influenza vaccination on the induction of protective serum antibodies in GPs (Vaccine 2006). Results showed some (non-statistically significant) effects on RTIs for the whole group and the authors feel that those results were more pronounced in the younger persons.
1. Did the authors perform a formal power analysis before analyzing these results, especially with regard to the subgroups?
Yes we did (as you can see after the remarks at the end of this letter), we considered several scenarios and several outcome measures. We agree that the study is underpowered for RTIs with positive nose and throat swabs, although you can discuss about the efficacy of the influenza vaccine needed to be clinical relevant. We think that among healthcare workers a higher efficacy is desirable especially in influenza cases with positive swabs,
because the most important benefit of the vaccine we expect is the prevention of transmission of influenza viruses to patients besides the protection of the HCW himself. If the power is too low, they should not look at different subgroups. The subgroups or more correctly the significant covariates were identified by means of a multivariate regression analysis. We agree that these results need to be confirmed in a bigger sample and an appropriate design. The discussion is adjusted.

2. What were the characteristics of the influenza seasons, and how intensive was the influenza activity? Figure 1 gives an idea of the influenza epidemics. In the second paragraph of the discussion we have given some characteristics.

3. Given the low numbers of participants and the low power to detect meaningful differences I believe there is too much speculation in the discussion on the potential factors influencing the negative findings. More emphasis should be placed on the effects on the more specific outcomes, notably the serological protection. For example, the outcome positive nose and throat swabs indicate much protection by the vaccine, but the study was imprecise. The discussion and conclusion are adapted.

4. I do not agree with their conclusion that the vaccine cannot benefit GPs. An efficacy of 50% is substantial and suggestions with regard to age can not be substantiated from the data simply because of limited power. Discussion and conclusion are adapted.

Overall, the authors should shorten their paper considerably and focus primarily on the specific and then on the RTI endpoint. They should recalculate the power and then make clear to the reader that there is efficacy and the study is too small to detect meaningful differences on less specific endpoints. Paper and discussion are adapted and shortened.

Reviewer 2: Herman J Bueving

Reviewer's report:

General
- The study is not blinded, the ethical argument the authors mention is not clarified and in my opinion questionable. The authors should describe the ethical arguments. Guidelines advise every GP to vaccinate himself each autumn to protect himself but also to protect his patients. We thought that GPs would refuse to participate in a blinded study or that the Ethical Board would have objections.

but this may have biased the results: GPs who were aware that they were vaccinated, may have reported fewer RTI symptoms for this reason (because they thought it could not be influenza). We didn’t ask GPs to register only RTIs with a possible diagnosis of influenza. We asked them to record every symptom of a RTI in general (reported RTIs in general were not different between vaccinated and unvaccinated GPs). They also could give their own diagnosis and indeed the vaccinated GPs were using the diagnosis of influenza less often, but this self-diagnosis was not used in the analysis.

- In the introduction the humoral response should be specified (IgA-hypothesis): the background is adjusted accordingly

- There may be GPs who did not vaccinate themselves, did the authors in any way controlled the vaccination? Vaccination was not controlled, but we instructed every GP to take a bloodsample just before and another bloodsample three to five weeks afterwards. The unvaccinated group only needed to give one bloodsample. When only one bloodsample was received in the vaccinated group the GPs were contacted to inquire for the reason: no
GPs didn’t forget to vaccinate themselves. In addition it was also their own choice and they only had to let us know.
- How did the GPs recalled the number of patients with influenza the last week? They had to record every day the number of influenza cases seen that day, in addition some of these patients were seen by the same GP for another reason a few days before (less than a week). Every GP could easily find the exact date of previous consults in the patient records.
- Results: what is meant by "an average highest body temperature", is it during influenza or during the season with a one time positive swab? Only while suffering from any RTI symptom the body temperature had to be taken. In consequence the highest body temperature registered during each RTI episode was considered in the analysis: the mean of these highest body temperatures was calculated. This is clarified in the text.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
- sample size: did the investigators calculate in advance how many GPs would be needed to detect a clinically relevant difference? Yes we did (as you can see after the remarks at the end of this letter), we considered several scenarios and several outcome measures. We agree that the study is underpowered for RTIs with positive nose and throat swabs, although you can discuss about the efficacy of the influenza vaccine needed to be clinical relevant. We think that among healthcare workers a higher efficacy is desirable especially in influenza cases with positive swabs, because the most important benefit of the vaccine we expect is the prevention of transmission of influenza viruses to patients besides the protection of the HCW himself. Cfr supra: answers to the first reviewer Eelko Hak.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- A native speaker should assist the authors. It seems to me that some phrases are Flemish-like or Dutch-like. 'High time to look closer into these issues'; 'collected by post'; "influence of several variables"; "general characteristics between GPs" are obvious examples. The text is corrected by International Science Editing, http://www.internationalscienceediting.com, as recommended by BMC medicine’s instructions for authors.
- figures 3,4,5 cannot be interpreted without the text, the age should be mentioned on the X-axis and the Odds ratio on the Y-axis. Only figure 4 will be presented in the text adapted on these remarks, figure 5 is given as an attached file; the text is adjusted accordingly.
- tables 1-3 should be a part of the text. Significant results are included in the text.
- In table 1 the phrase 'child and family preventive medicine' should be clarified: this is changed in the table and the text as follows: working in a Child and Family preventive medicine facility.
- table 3: roman superscripts, but arabic footnotes. This is corrected.
- 'vaccine when age is 30 years’ / 'vaccine when age is 50 years’ is confusing: are these age boundaries? Our regression models contained the variable of interest (= vaccination yes or no), several confounding variables (including age in years) and significant interaction terms with vaccination. Only vaccine*age was significant and in consequence the effect of vaccination can only be descript in terms of exact age. For example we calculated the effect size (OR) of vaccination when age was exactly 30 years and 50 years.
- in the text describing these age-specific results, the same problem
arises: “influenza vaccination of a young GP (30 years old)…” The text is adjusted accordingly.
- how was the age distribution of the participating GPs? (%<30, 30-40, 40-50, >50?)

<table>
<thead>
<tr>
<th>2002 and 2003</th>
<th>&lt;30 y</th>
<th>30-39y</th>
<th>40-49y</th>
<th>50-59y</th>
<th>&gt;59y</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vac</td>
<td>18</td>
<td>35</td>
<td>65</td>
<td>39</td>
<td>5</td>
<td>162</td>
</tr>
<tr>
<td>Unvac</td>
<td>18</td>
<td>16</td>
<td>26</td>
<td>13</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>51</td>
<td>91</td>
<td>52</td>
<td>7</td>
<td>237</td>
</tr>
</tbody>
</table>

Chi-square test: p = 0.1

- the discussion is extremely long discussion section is changed and shortened where possible
- vaccinating children of GP’s could be worthwhile! probably this is right, but because of the long discussion we have chosen not to mention this in the text
- it should be stressed that taking neuraminidaseinhibitors is only advisable in case of an epidemic added in the text

Reviewer 3: Mary Patricia Nowalk
Reviewer’s report:
General

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
There are four major areas for improvement in this paper:
1. It would benefit from clearer, crisper writing. For example, some words are incorrectly used and some sentence structure is confusing. I suggest using more headings and subheadings, numbers within lists in the text and careful proofreading. Text is adapted and English proofreading will be performed by International Science Editing, http://www.internationalscienceediting.com, as recommended by BMC medicine’s instructions for authors.
2. Table 1 would benefit from rearrangement of the data into four columns of data: Vaccinated 2002, Unvaccinated 2002 and Vaccinated 2003, Unvaccinated, 2003. Symbols for non significant values should not be included. Table is adapted
3. Table 2 should have labelling consistent with table 1 and significant values should be bolded. Alternatively, given that there is very little significant data in this table, it might be better presented in the text and eliminating the table. This table shows the direct answers to the research questions: for this reason we believe that presenting this table is essential for the understanding of the study results.
Note: we noticed some mistakes in the numbers which we corrected
4. Table 3 - too many footnotes and they are not consistent. Table is adapted
5. Figure 2 does not show a clear pathway from the initial study sample to the final sample used for analysis. It should not be in a table form. Figure is adapted.
6. There are too many figures for the amount of data and size of the study. Perhaps Figures 3,4 and 5 could be combined? Only figure 4 shall be presented. Figure 5 is given as an attached file.
2. The title is misleading. I would not consider this study to be a controlled trial. Physicians self selected vaccination or not and were asked to self swab when they had symptoms of
RTI. We agree that the term controlled trial must be used carefully and we discussed the use of this label before submitting the paper, but the following definitions given by the Cochrane Library Glossary (http://www.cochrane.org/resources/glossary.htm) justifies the use of the term controlled trial in our study.

**Clinical trial**
An experiment to compare the effects of two or more healthcare interventions. Clinical trial is an umbrella term for a variety of designs of healthcare trials, including uncontrolled trials, controlled trials, and randomised controlled trials. (Also called intervention study.)

**Control**
1. [In a controlled trial:] A participant in the arm that acts as a comparator for one or more experimental interventions. Controls may receive placebo, no treatment, standard treatment, or an active intervention, such as a standard drug.

**Controlled trial**
A clinical trial that has a control group. Such trials are not necessarily randomised.

It is unknown why those who did not swab, failed to do so, were they too sick? Did they stay home and not have the swabs with them? No, this is not the case for the following reasons. Most GPs have their practices at home and when we compare the body temperature and sick leave (as indicators of the level of sickness) between those who did take the swabs and those who didn’t: there was no statistical difference for the two groups for the two variables. 3. Small sample size and large loss of data, especially in year 2 weaken the data and the conclusions that can be drawn. How many of the GPs were in each age group? were there sufficient?

<table>
<thead>
<tr>
<th></th>
<th>&lt;30y</th>
<th>30-39y</th>
<th>40-49y</th>
<th>50-59y</th>
<th>&gt;59y</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>39</td>
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<td>162</td>
</tr>
<tr>
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<td>26</td>
<td>13</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>51</td>
<td>91</td>
<td>52</td>
<td>7</td>
<td>237</td>
</tr>
</tbody>
</table>

Chi-square test: p = 0.1
The paper would benefit from clearer description of statistical analyses. Text is adapted. 4. The conclusions are rather strongly stated, given that this is a small study and presumably the only one of its kind. Conclusions are adapted, also accordingly with the remarks of the first reviewer Eelko Hak.

**Sample size estimation**

**General remarks:**
The expected frequency of influenza defined in several ways is dependable on several factors.: the basic immunity (humoral, serological and cell-mediated), the kind of circulating influenza strains (the same during several years or rather new) and the match between vaccine and circulating strains. Therefore it is extremely difficult to predict the sample sizes needed. We assumed that between 60 to 70% of the GPs would choose to be vaccinated against influenza each year. So we opted for a 2:1 design. We decided to accumulate at least the results of two consecutive winterperiods.

**Outcome: RTI with fourfold titre rise**
In the study of Wilde [1] among healthcare workers (period 1992-1995) a mean of 13.9% non-vaccinated and 1.7% vaccinated HCW showed a seroconversion and in the study of Elder [2] 23% of the unvaccinated healthcare workers had a seroconversion after the flu epidemic. In the Textbook of Influenza [3] an efficacy of an influenza vaccination among healthy adults between 70 and 90% is mentioned if a good match exists between the circulating virus strain and the vaccine. In years of mismatch the efficacy drops to 40-60%.

**Outcome: RTI with positive nose and throat swabs**

We found no direct studies, which could give estimates about the efficacy of an influenza vaccination on influenza cases with RT-PCR positive nose and throat swabs. In our pilot study among unvaccinated GPs we found 8.5% positive swabs (2001-2002). As in cases of serological defined influenza efficacy of 70-90% can be considered of clinical significance.

**Outcome: RTI (clinical diagnosed including slight symptoms)**

In the study of Nichol [4] 61% of the vaccinated and 69% of the unvaccinated healthy adults had at least one upper respiratory illness during one influenza period (1994-1995).

Via Epi-info calculations this estimates give following sample sizes for a power of 80% and a two-sided significance level of 0.05:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage in unvac GP</th>
<th>Percentage in vac GP</th>
<th>Efficacy</th>
<th>Sample size unvac</th>
<th>Sample size vac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology pos</td>
<td>13.7</td>
<td>4.2</td>
<td>70%</td>
<td>109</td>
<td>218</td>
</tr>
<tr>
<td></td>
<td>13.7</td>
<td>1.4</td>
<td>90%</td>
<td>48</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>6.9</td>
<td>70%</td>
<td>62</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>2.3</td>
<td>90%</td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td>Pos swabs</td>
<td>8.5</td>
<td>2.6</td>
<td>70%</td>
<td>184</td>
<td>368</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>0.9</td>
<td>90%</td>
<td>96</td>
<td>193</td>
</tr>
<tr>
<td>RTI clin pos</td>
<td>69</td>
<td>61</td>
<td>30%</td>
<td>439</td>
<td>878</td>
</tr>
</tbody>
</table>

**Posthoc sample size calculations:**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage in unvac GP</th>
<th>Percentage in vac GP</th>
<th>Efficacy</th>
<th>Sample size unvac</th>
<th>Sample size vac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology pos</td>
<td>19.7</td>
<td>5.0</td>
<td>75%</td>
<td>64</td>
<td>127*</td>
</tr>
<tr>
<td></td>
<td>19.7</td>
<td>2.0</td>
<td>90%</td>
<td>40</td>
<td>79*</td>
</tr>
<tr>
<td>Pos swabs</td>
<td>14.5</td>
<td>8.3</td>
<td>42%</td>
<td>322</td>
<td>644</td>
</tr>
<tr>
<td></td>
<td>14.7</td>
<td>4.4</td>
<td>70%</td>
<td>104</td>
<td>208</td>
</tr>
<tr>
<td>----------------</td>
<td>------</td>
<td>-----</td>
<td>------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Serology and</td>
<td>14.7</td>
<td>1.5</td>
<td>90%</td>
<td>54</td>
<td>108*</td>
</tr>
<tr>
<td>pos swabs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.8</td>
<td>11.3</td>
<td>58%</td>
<td>80</td>
<td>161*</td>
</tr>
<tr>
<td></td>
<td>26.8</td>
<td>8.0</td>
<td>70%</td>
<td>52</td>
<td>104</td>
</tr>
<tr>
<td>RTI clin pos</td>
<td>53.3</td>
<td>52.5</td>
<td>2%</td>
<td>Not relevant</td>
<td>Not relevant</td>
</tr>
<tr>
<td></td>
<td>53.3</td>
<td>37.3</td>
<td>30%</td>
<td>122</td>
<td>243</td>
</tr>
</tbody>
</table>

* This estimate was reached in our study (177 vac/ 75 unvac = 262)

**Conclusion**

The actual sample size is capable of demonstrating a clinical significant difference in occurrence of RTIs with a fourfold titre rise with or without RTIs with positive swabs. Only if we assume a clinical relevant efficacy of 90% on the occurrence of RTIs with influenza positive nose and throat swabs our sample size is appropriate. Clinical RTIs with an imprecise definition of influenza cannot demonstrate an effect of influenza vaccination.


