Author's response to reviews

Title: An open-label randomized clinical trial of prophylactic paracetamol co-administered with 7-valent pneumococcal conjugate vaccine and hexavalent diphtheria toxoid, tetanus toxoid, 3-component acellular pertussis, hepatitis B, inactivated polio virus, and Haemophilus influenzae type b vaccine

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Version: 2 Date: 21 September 2012

Author's response to reviews: see over
Dear Editor:

Enclosed for your consideration for publication in *BMC Pediatrics* is the original manuscript, “*An open-label randomized clinical trial in children of prophylactic paracetamol co-administered with 7-valent pneumococcal conjugate vaccine and hexavalent diphtheria toxoid, tetanus toxoid, 3-component acellular pertussis, hepatitis B, inactivated polio virus, and Haemophilus influenzae type b vaccine.*”

We submitted a longer version of this manuscript in December 2011, MS: 9028013996526958, which was peer reviewed. At that time, the journal felt that the revisions to the manuscript would require longer than the standard revision period, but indicated that it would be possible to revise our manuscript to address the reviewer’s comments, after which the journal would be willing to reconsider our manuscript. Therefore, we have addressed the reviewer’s comments, and would like to resubmit the revised manuscript as a new manuscript to *BMC Pediatrics*.

A detailed response to the reviewer’s comments is included below the signature line to accompany the revised manuscript. All authors have contributed to and approved the manuscript for submission, and the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

**Competing interests**
MAR and SZ are consultants to Wyeth/Pfizer Inc and have received travel grants or honoraria within the past three years. Pfizer paid the article-processing charge for this article. CJ, BS-T, and WCG are employees of Pfizer Inc. SB was an employee of Wyeth, which was acquired by Pfizer Inc in October 2009.

If you require any additional information, please let us know. We look forward to receiving your decision regarding publication.

Sincerely,

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Reviewer comments of “An open-label randomized clinical trial in children of prophylactic paracetamol co-administered with 7-valent pneumococcal conjugate vaccine and hexavalent diphtheria toxoid, tetanus toxoid, 3-component acellular pertussis, hepatitis B, inactivated polio virus, and Haemophilus influenzae type b vaccine”
Version: 2
Date: 4 April 2012

Reviewer 1 (Roman Prymula)

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I have received reimbursements, fees and funding from GSK, Wyeth, Aventis Pasteur. I do not have any other conflict of interests.

Reviewer's report:

Comment 1: There is substantial time delay between end of the trial and publication what underlines the major weakness of the paper - lack of immunological data. If the data would be presented immediately after completion and processing, evidence about influence on lower immunogenicity was not known. Authors should explain why the publication is so late.

Response: You are correct in pointing out the age of the trial and delay in submitting the manuscript. The publication is late due to the time constraints of the lead investigators, who are practicing physicians, to write the manuscript and the lengthy review times required by coauthors.

Comment 2: Generally article brings limited added value to already existing level of knowledge. Data with immunological outcomes would be much more appreciated now. Based on purely technical aspects I do not have objections and way how the paper is processed is appropriate.

Response: We agree that collecting data on the immunological response would add value to the study. However, at the time the study was designed, our research question was led by a different observation; i.e. low-grade fever was observed more frequently in two clinical trials (Knuf et al; Olivier et al) after co-administration than after single administration of two recommended pediatric vaccines. Therefore, the objective of the study was limited to investigating the efficacy and safety of prophylactic use of paracetamol to prevent fever after administration of routine pediatric vaccines.

References


Reviewer 2's report (Moshe Ipp)

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: 'I declare that I have no competing interests'.

Reviewer's report:

Comment 1: Thank you for asking me to review this manuscript. The manuscript is well presented but would suffice as a short communication; the word count is 3812 and could be made shorter for reader friendliness, even though it will be open access.

Response: We agree that the manuscript could be shortened and more to the point. We have reduced the text to <2000 words in our revised manuscript.

Comment 2: There is a paucity of new information, however. The research question being asked (the primary objective) is not original. The effectiveness and safety of prophylactic analgesic/antipyretic medication for infant and toddler vaccination has been published before with similar results. Essentially, analgesic/antipyretics are effective in reducing fever and other minor reactions when used prophylactically at the time of infant and toddler vaccination (Author’s references 3, 4, 6, 10). Fever above 39°C was uncommon in both groups.

Response: We agree that there are some similar studies in the literature. However, we feel that the controlled, multicenter design (22 pediatric practices in Germany), the inclusion of both infant and toddler doses for analysis, the newer vaccines assessed, and the e-diary reporting of temperature readings over a 4-day period adds meaningful data to the body of literature on this subject.

Comment 3: What is new in this study: An updated confirmation of effectiveness and safety of prophylactic analgesic/antipyretic medication given at the time of vaccination when one or more (newer) vaccines are administered. Large multicenter study – 22 sites; The analysis of two groups – ITT and PP.

Response: We appreciate this assessment, and feel that this study adds to the literature on this topic.

Comment 4 (a-d below): What the authors do not include in the methodology or results, and which are potentially important variables often used in this type of study:

Comment 4a: Standardization of intramuscular vaccine injection across sites

Response: The vaccine was given as described on page 6. No further details were stipulated by the protocol.

“Subjects received PCV7 (Prevenar®, Pfizer Inc; containing pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and DTPa-HBV-IPV/Hib (INFANRIX hexa™, GSK) at ages 2, 3, and 4 months (infant series) and at age 11–14 months (toddler dose) as 0.5 mL intramuscular injections into the left and right anterolateral thigh, respectively.”

Comment 4b: Details on needle length, needle gauge (16 or 25 mm? 23 - 27 gauge?)

Response: Needle length was not specified in the protocol.

Comment 4c: Type of thermometer used to take subjects temperature

Response: A digital thermometer was used to take the core rectal temperature. This is now described on page 6.

Comment 4d: Use of ‘therapeutic antipyretic medication’ particularly in the control group

Response: The results of ‘therapeutic antipyretic medication’ have been added to the manuscript. The following text was added to the methods on page 6:
“If required for therapeutic purposes, paracetamol was to be offered to the participants at the investigator's discretion. To prevent overdose, subjects in the prophylaxis group were not to receive paracetamol in addition to their study medication on the day of vaccination or sooner than 6 hours after their last dose. “

**Comment 5 (a and b below): Major limitations**

**Comment 5a:** Lack of immunogenicity data. This is addressed by the authors in their discussion of limitations. They conclude that even though they never measured antibody responses (which would have added substantially to the manuscript), there is one previous published study that has shown a reduction of several antibody responses when Paracetamol it is used prophylactically at the time of vaccination (ref 10). Even though the clinical significance of these observations is unknown, this finding remains potentially the most compelling reason not to recommend the use of routine prophylactic Paracetamol.

**Response:** We agree that collecting data on the immunological response would have added value to the study. However, at the time the study was designed, our research question was led by a different observation; i.e. low-grade fever was observed more frequently in two clinical trials (Knuf et al; Olivier et al) after co-administration than after single administration of two recommended pediatric vaccines. Therefore, our objective was limited to investigating the efficacy and safety of prophylactic use of paracetamol to prevent fever after administration of routine pediatric vaccines. A similar Pfizer follow-up study is ongoing, which addresses this limitation.

**References**


**Comment 5b:** In addition, although prophylactic Paracetamol was shown to be effective in this study in reducing febrile reactions, these mild reactions were of minor importance to parents and do not justify the use of routine prophylactic medication.

**Response:** We agree with this opinion, which is now clearly stated in our conclusions.

“The data confirm current recommendations that analgesic/antipyretics should be given only to treat clinically relevant postvaccination symptoms and not for routine prophylaxis.”

**Recommended changes before publication:**

**Comment 6:** Abstract: State the objective in the background not in the methods

**Response:** We agree, and made this change to the abstract on page 3 (highlighted).

**Comment 7:** Conclusion should be the first sentence only. The second sentence has nothing to do with this study

**Response:** We agree and removed all but the first sentence.

**Comment 8:** Methods: Include B, 1 -4, above if available

**Response:** These are included as responses to the comments above, 4a-d.
Comment 9: Tables: Too many. Too cumbersome. These should be condensed.
Response: We agree, and consolidated / removed some of the tables.
Comment 10: Discussion: It is becoming generally accepted that analgesic/antipyretics should only be used for those infants and toddlers (a minority) who experience post-vaccination irritability, pain etc. with or without fever. Not for routine prophylaxis. This should be stated explicitly in the discussion.
Response: We agree, and state this clearly in the revised manuscript:
“The data confirm current recommendations that analgesic/antipyretics should be given only to treat clinically relevant postvaccination symptoms and not for routine prophylaxis.”
Comment 11: Conclusion: Only the first two sentences and the last sentence are relevant to this study. The rest should be under the discussion section.
Response: We agree, and moved the information about immune responses to the discussion section.
Reviewer 3’s report (Lisa Jackson)

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I have received research funding (to my organization) for the support of vaccine clinical trials, and travel support, from Pfizer.

Comment 1: This is an interesting paper reporting the results of an open label randomized trial of paracetamol prophylaxis among infants receiving PCV7 and DTPa-HBVIPV/Hib vaccines.

Response: Thank you for your comment.

Major Compulsory Revisions

Comment 2: Given the relatively high rates of fever in the control group, it would be interesting to evaluate an intermediate fever cut-off of temperature ≥ 38.5°C.

Response: Unfortunately, this was not included as an end-point of the study at the time of preparing the protocol and the statistical analysis plan.

Comment 3: The rates of fever following co-administration of the vaccines evaluated is somewhat concerning, particularly the rate of temp > 39°C in the toddler control group of approximately 13%. Further discussion of the reactogenicity of this vaccine combination is warranted, particularly if prophylaxis is not advisable.

Response: We agree, and added the following to the discussion, pages 10–11 (see highlighted text):

“Fever >39 °C was rarely observed after the infant series and occurred in approximately 13% of the control group after the toddler dose. However, exposure of a whole population to prophylactic antipyretics to prevent fever in the minority does not seem justified, whereas targeted treatment of symptoms would reduce the number unnecessarily exposed to the risk of toxicity.”

Comment 4: The apparent effect of the intervention on local reactogenicity is different than reported in some other studies (e.g., Jackson et al. Pediatrics. 2006 Mar;117(3):620-5). A more detailed discussion of these findings would be of interest.

Response: We agree that more discussion would be of interest on this topic, and added the following to the discussion section on page 10 (see highlighted text):

“Two studies in children aged 4–6 years who received a fifth dose of DTaP, or a booster dose of DTwP reported no significant impact of paracetamol on the incidence of local reactions [4, 9]. Local reactions in children generally occur more frequently after a booster dose such that the weak anti-inflammatory mechanism of paracetamol may not be sufficient to control inflammation, suggesting that ibuprofen may be a better alternative if required [10].”