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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BMC Pediatrics
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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 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 were 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.
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-componentacellular pertussis, hepatitis B, inactivated polio virus, and Haemophilus influenzae type b vaccine”

Reviewer (Lode Schuerman)
Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I am an employee of GSK Vaccines

Reviewer's report:
Major Compulsory Revisions:
1. It is not clear from the abstract how the final sentence in the conclusion is based on the results. On the contrary, the results confirm that prophylactic use of “paracetamol effectively prevented fever and other reactions”, so based on this it is not clear in the abstract why it is concluded that paracetamol should be used “to treat symptoms only and not for routine prophylaxis”. If the rate of fever >39°C following the toddler dose is 13% and prophylactic paracetamol allows to reduce this to less than 5% as indicated by your data, should it then be concluded that this is not recommended? The fact that this should not be recommended is based on other elements that are discussed in the body of the manuscript, but not in the abstract. In addition, isn’t the current uncertainty about potential impact on immune responses also discouraging routine paracetamol prophylaxis?

Response: The authors agree with the reviewer’s comments. However due to the importance of the current recommendations on antipyretic use within the conclusion, the authors prefer to retain their conclusion. This decision is supported by a previous reviewer, Moshe Ipp, who pointed out in his review of this article, that “these mild reactions were of minor importance to parents and do not justify the use of routine prophylactic medication.”

The wording of the abstract conclusion has been changed from “confirm” to “support”, which seems more appropriate.

Conclusion: Paracetamol effectively prevented fever and other reactions, mainly during the infant series. However as events were generally mild and of no
concern in either group, our data support current recommendations to administer paracetamol to treat symptoms only and not for routine prophylaxis.

2. Numbers don’t seem to match between Figure 1 and Table 2. For example, why is the denominator for fever #38°C in the ITT cohort only 100 for the infant series in the prophylactic group, whereas there are 145 children in that group that received the 3 primary vaccine doses, and why are there only 80 children in the PP analysis whereas there were 116 included in the PP cohort? Also, it is not clear why the denominator for fever #38°C is different from the denominator for fever >39°C.

Response: Figure 1 gives an overview of the number of subjects who received study vaccine throughout the study, and also gives an overview of the number of subjects who were to be included in the overall intent-to-treat population and per-protocol population. However these are not the final numbers for the analysis of the intent-to-treat population and per-protocol population. As described below for analyses additional subjects were excluded, depending on availability of fever data for each subject.

The Intent-to-Treat Population (ITT) included any randomly assigned subject, with or without fever #38°C who had at least 1 recorded postvaccination temperature. However the number of subjects included in the ITT analysis of fever was dependent on whether missing data was present or not. To be counted as not having a fever, all temperature measurements were required. Thus, if a subject’s highest temperature was 38.5°C and had at least 1 missing temperature measurement, then this subject would be included in the analysis of fever #38°C and excluded from the analysis of fever >39°C. Inclusion of subjects with missing data as “absent” (no fever) would otherwise lower the rate of fever reported in this manuscript. So, the current method of dealing with missing data is a conservative approach, and may slightly overestimate the true fever rate. This same logic applies to defining the per protocol analysis population.

The authors agree that this has not clearly been presented in the manuscript and have added clarifications to the Flowchart and the manuscript.

Analyses Populations

The Intent-to-Treat Population (ITT) included any randomly assigned subject, with or without fever #38°C who had at least 1 recorded post vaccination temperature. However a decision to include subjects in the actual ITT analysis of fever (denominator N) was dependent on whether or not data was missing. To be counted as not having a fever, all temperature measurements were required. Thus, if a subject’s highest temperature was 38.5°C and had at least 1 missing temperature measurement, then this subject would be included in the analysis of fever #38°C and excluded from the analysis of fever >39°C. Inclusion of subjects with missing data as “absent” (no fever) would otherwise lower the rate of fever reported.

The per protocol (PP) population included subjects who received their allocated medication, all four doses of study vaccine, and had a sufficient number of temperatures recorded to permit evaluation. For handling missing data the same
logic as for the ITT population was applied.

The safety population included all subjects who received at least one dose of study vaccine. Subjects who lacked any safety data (AE, reactogenicity, or temperature) for a particular vaccination were excluded from that analysis. Separate safety populations were defined for each vaccination.

More detailed explanations of the analyses which were considered by the authors as too detailed for this manuscript are described below (Section 2.1.5 of the Statistical Analysis Plan, 24 May 2007):

3. Numbers in Table 4 don't match numbers in Table 2 either. How does the fever reported for the entire infant series in Table 2 relate to the fever reported for each of the vaccine doses in Table 4? But even for the toddler dose there is a difference between Tables 2 and 4. For example in the prophylactic group Table 2 reports 58 children out of 108 with fever #38°C, whereas Table 4 reports 53 children out of 103 with fever #38°C to #39°C plus 4 children out of 87 (why again a different denominator) with fever >39°C to #40°C.

Response: Table 2 reports on the “ITT and PP Analyses Populations which included subjects who qualified for the efficacy analysis” which differed from Table 4 which reports on the “Safety Population and analysis of safety”.
Numbers in Table 2 have been derived for the ITT population as described above where N = number of children in the analysis; n = number of children with the specified degree of fever.

Numbers in Table 4 are taken from the Safety Population. The safety population included all subjects who received any study vaccine. Subjects who lacked any safety data (AE, reactogenicity, or temperature) for a particular vaccination were excluded from that analysis. Separate safety populations were defined for each vaccination. In the tables n = number of subjects experiencing the event and N = number of subjects reporting "yes" for at least 1 day or "no" for all days. For the safety analyses, participants were analyzed according to the vaccine actually received: 7vPnC with paracetamol or 7vPnC without paracetamol. Definitions of n/N and have been included in the Table footnotes.
More detailed explanations of the safety analyses which were considered by the authors as too detailed for this manuscript are described below (Section 2.1.6.4 of the Statistical Analysis Plan, 24 May 2007):

4. Abstract, line 7: “heptavalent” should be “hexavalent”
Response: Text has been corrected.

Minor Essential Revisions:
5. Are numbers in Tables 3 and 4 ITT or PP? Please specify.
Response: Numbers in Table 3 and 4 are from the safety population. This has now been added to the titles of the tables.

6. According to Figure 1, there seems to be an imbalance between both groups in terms of temperature measurement compliance. Given that measurement of body temperature will probably not be omitted for children developing fever, shouldn’t the potential of a bias reducing the efficacy of prophylactic paracetamol be discussed?
Response: The authors agree that there is a potential of a bias reducing the efficacy of prophylactic paracetamol due to the very conservative approach taken of handling missing data which has a potential impact on reducing efficacy. True efficacy may be higher than what this manuscript reports.

The discussion now includes:
Due to the very conservative approach taken of handling missing data, the incidence of fever reported in this manuscript is probably an over-estimate of the true rate. Inclusion of subjects with missing data would have lowered the rate of fever reported. So that there is a potential of a bias, which may have caused a reduction in assessment of efficacy of prophylactic paracetamol. True efficacy may be higher than what is reported here.

7. Prophylactic paracetamol seemed to also have reduced SAEs? Shouldn’t this be commented in the discussion? Does this make sense looking at the type of SAEs, or is this just a chance finding?
Response: The authors apologize for an error which has occurred in this section. Seventeen serious adverse events (SAEs) were reported in 10 children (three children in the control group and seven in the prophylaxis group). The text has been corrected accordingly. In this case prophylactic paracetamol did not reduce the incidence of SAEs.
Reviewer (Robert Chen)
Level of interest: An article whose findings are important to those with closely
Reviewer’s report: This paper reports the findings of an open label study of efficacy and safety of ~300 healthy infants randomized to routine pediatric vaccination in Germany with or without prophylactic use of paracetamol. The study itself was started in March 2005 and the current paper represents a shortened version of a previous submission, addressing the prior reviewer comments. The current paper satisfactorily addresses the comments of prior reviewers.

Minor essential revision:
Since fever is a key outcome in this study, the Methods should explicitly state to what extent this study was or was not able to follow the Brighton Collaboration case definition for fever (PMID:14741143).

Response: The authors agree to include reference to the Brighton Collaboration case definition (Vaccine 22 (2004) 551–556) in the Methods:
Fever was defined as the endogenous elevation of at least one measured body temperature of #38°C [Reference: Brighton Collaboration Working Group. Vaccine 22 (2004) 551–556].

Reviewer (Roman Prymula)
Reviewer’s report: Generally manuscript was reprocessed and adapted according to reviewers’ comments. All the major issues have been addressed. In spite of fact the major limitation, lack of immunogenicity data, is not possible to improve and conclusion is not quite original I recommend publishing.

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

Response: Thank you for your comment.

Additional note:
As per request of the journal editor (Emily Crow, PhD) we have added a statement of informed consent to the Methods, as follows: Written informed consent was obtained from parents/legal guardians from all subjects before enrollment.