Reviewer’s report

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

Version: 2 Date: 2 January 2013

Reviewer: Lode Schuerman

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?

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.

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.

4. Abstract, line 7: “heptavalent” should be “hexavalent”

Minor Essential Revisions:

5. Are numbers in Tables 3 and 4 ITT or PP? Please specify.
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? The same is true for children not receiving all paracetamol doses according to protocol, since this is most likely only excluding children without fever.

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?

**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