Author's response to reviews

**Title:** Perception and management of fever in infants up to six months of age: A survey of US pediatricans

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**Author's response to reviews:** see over
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Editor
Melissa Norton, MD
BMC Pediatrics
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Dear Dr. Norton:

On behalf of all authors, please find enclosed the revised manuscript entitled, “Perception and management of fever in infants up to six months of age: A survey of US pediatricians” for consideration for publication in BMC Pediatrics.

We have revised the manuscript (all revisions in the manuscript are in blue and red) based on the comments and suggestions of the reviewers. Below you will find our detailed responses (in red) to the reviewers' comments with references to the changes in the manuscript. We feel that we have addressed the reviewers' comments and that this manuscript will be of particular interest to the audience of BMC Pediatrics.

The content of the manuscript represents the views of all of the co-authors. The submitted manuscript has not been published and is not under consideration for publication elsewhere. This study was supported by Merck & Co., Inc.

Please do not hesitate to contact me if you have any questions. I am looking forward to hearing from you soon.

Sincerely,

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Title. Perception and management of fever in infants up to six months of age: A survey of US pediatricians

Reviewer # 1

Major concerns
Major concern is that it seems implied that the study refers to a hypothetical well-appearing infant with a fever without a source, but this should be specified.

This was added to the "Survey Design" section on page 8.

Another concern is that in the manuscript is focused on the definition of fever severity based on its level and infant’s age. Although in special circumstances high fever may be a predictive factor for severe bacterial infection (such as a high white blood cell count or high levels of C-reactive protein), especially in children under three months of age, in itself, the degree of fever should not be taken as an indicator of the risk for severe disease (Chiappini E et al. Clin Ther 2009;31:1826-43). Some studies in children have found a correlation between a body temperature >41.1°C and the risk of bacteremia and invasive bacterial infection, whereas others have not. Taken alone, a high body temperature (>39°C) has very low sensitivity and specificity for severe bacterial infection. This is a limit of the study and should be specified.

This limitation was added in the discussion section on page 16 and added reference 15.

Introduction
Definition of fever is oversimplified. It should be specified that it is an elevation of the body temperature above the normal range secondary to a modification of the thermoregulatory center set-point in the hypothalamus.

We based our definition on the one given by Medical Dictionaries such as The Bantam Medical Dictionary (Third Edition, 2000). The definition we used is commonly used in the literature.

The sentence “ACIP recommend administration of up to 9 different vaccine antigens during the six months of life”, although true, may sustain the misconception that many vaccines are dangerous and may overload or weak the infant immune system. Pediatricians must play a central role in correcting this misconception and should educate worried parents regarding vaccine safety. It should be noticed that fever after immunization is a common event but high fever (greater than 39.5°C) is an exceptional event occurring in 1% of infants (Prymula R. Lancet 2009;374:1339-50). This observation should be taken into account when examining an infant with high fever after immunization because this child is at high risk of infection and should be appropriately managed. The
message that infants with fever after immunization are at low risk of infection may be confounding.

A statement was added on page 5 to emphasize that fever after immunization is common, however high fever is less common. The citation of Prymula was also added.

When summarizing practice guidelines for the management and treatment of febrile infants (page 5, line 19) other references should included in the list besides the US guidelines (i.e. NICE guidelines, WHO guidelines.)

Although other references would be valuable, the focus of this manuscript is on US guidelines. We clarified the text and added "US practice guidelines" on page 5.

Methods
It should be specified how fever would be recorded (site and thermometer type) and if the survey refers to a well-appearing infant with a fever without a source.

The pediatricians were asked to assume that the temperature was taken by rectal measurement. The thermometer type was not specified. This was clarified on page 8 under the survey design section.

Randomization method is not described. Please provide details regarding the procedures you used to obtain random samples of pediatricians.

The random samples were generated by a computer. We also added more explanation on how the random samples were drawn. This was clarified on page 7.

Results
Page 10, last line. Age should be better expressed as median and interquartile range instead of mean and standard deviation. Figure 1 is clear but for more clarity we suggest to report the proportion of pediatricians answers (and respective 95% CIs) in the text or in one table since it does not appear anywhere.

We added the median age in the results section on page 10. The proportion of respondents to each of the questions was 100% (out of 400 responders). This was because the survey was programmed into a Web-based application hosted with redundant fail-over Web servers and databases to ensure availability and reliability and to ensure that responders cannot skip questions. For clarity, we added the confidence intervals on Figure 1 as suggested by the reviewer.

Discussion
Discussion should be expanded.
It should be underlined that these results may have practical implication for the organization of the emergency department in not-office hours and that educational programs for the management of fever in infants are needed in US.

The statement "These results may have practical implications for the
organization of the emergency departments during off-office hours and may suggest that specific educational programs for the management of fever in infants are needed in the US.” was added on page 15.

It should be also focused what is the authors’ opinion regarding the different approach to the infant with fever according to his/her recent previous immunization status (i.e.: this strategy may pose the infant at risk since he/her may have a severe bacterial infection and diagnosed may be delayed).

The focus of this manuscript was not to provide any guidelines for fever management; rather it was meant to inform the readers on contemporary US pediatricians' perception and referral practices to ER and hospital admissions related to fever management in infants. It is not designed to provide guidance on treatment practices. This was clearly stated in the background section of the manuscript on page 6. This is why we opted not to discuss our opinions on approaches to management fever in infants after getting their immunization.

It should be stressed the concept that high fever after immunization is rare (about 1% of cases) and these infants are at risk of a bacterial infection.

This was stated on page 14 in the discussion section as "Data collected from routine childhood vaccines have shown that fever typically occurs in 1%-10% of infants after vaccination, but the rate can increase as high as 30% to about 50% among those who received multiple vaccines."

Also it should be noticed that the workup of these infants should include at least an urine test and that all febrile newborns (aged < 28 days) should be always hospitalized.

We acknowledge the importance of testing; however the scope of the manuscript is not to provide guideline for fever management or testing.


We added a paragraph on page 16 to discuss the above mentioned papers and highlight the fact that the attitude of pediatricians toward managing febrile infants is changing after the introduction of the pneumococcal conjugate vaccine.

The attitude to prescribe antipyretics at a certain body temperature level should be discussed, since it is not recommended the AAP, NICE, WHO and the Italian guidelines for the management of fever in children (Richardson M et al. NICE
generally, the use of antipyretics in children is recommended only when the fever is associated with evident discomfort (eg, prolonged crying, irritability, reduced activity, reduced appetite, disturbed sleep) and not for a given level.
The fact that response to antipyretics is not a predictive factor for the cause of fever should be also remembered here.

We expanded the discussion to include a paragraph on the use of antipyretic for fever management.

**Conclusions** also should be focused on the need of implementing educational programs for US pediatricians in order to reduce fever-phobia but also to manage properly febrile infants.

We added the statement "These results may be valuable when developing fever management guidelines and when..." in the conclusion on page 16.

Table 1.
Heading is no clear to the reader. (N/Mead; %/SD?). I suggest to summarize results in one column (i.e. Mean and SD or, better, median and interquartile range)

We revised the Table by including only (N) and (%) in the heading.

**Minor essential revisions:**
Abstract
95% Confidence interval should be abbreviated as 95%CI not CI

We revised the abstract accordingly on pages 3 and 4.

Introduction
Page 6, lines 3-6 need a reference. The paper by Chiappini et al (BMC Public Health 2009;9:300) demonstrating that the approach to the febrile child may be influenced by his/her PCV vaccination status, is in contrast with guidelines recommendations, should be cited here.

We added the reference as suggested

Page 6, line 4. Bacteria’s names should be written in Italics and correctly (i.e.: Streptococcus pneumoniae)

We revised the writing of bacteria as suggested
Page 6. line 10. Perception of fever according to internal body temperature: internal BD is not routinely measured but it is estimated by the use of thermometers placed rectally, axillary,… Perhaps the word “internal” should be eliminated.

We deleted "internal" as suggested.

Methods
The first time the word “confidence interval” is used should be followed by its abbreviation (95%CI page 9 last line) and afterwards the abbreviation should be used.

We revised the abbreviation for the 95% CI as suggested throughout the manuscript.

Results
Please specify the proportion of paediatricians who answered to survey out of the total number of paediatricians who were contacted (401/17392= 2.3%).

We did not specify the proportion of pediatricians who answered the survey because the design itself of the survey meant a measurement of the true response rate was not possible. (the fact that we halted the administration of the survey once we reached the total number of 400 respondents.) We addressed this in the discussion section.

Discretionary revisions
Introduction
Fever phobia among parents is a major issue. It should be remembered that physicians may contribute to reduce it educating the family and illustrating that fever is a normal physiologic response to an infection and should give detailed information regarding how to manage it.

This is a relevant point regarding pediatric practice, but out of scope of the current manuscript.

Reviewer # 2
The topic of fever management in children 0-6 months is an important issue for primary care and ED pediatric providers. Management of fever is further influenced by our successful vaccination efforts against Hib, pneumococcus, and possible meningococcus. I applaud you on analyzing such a large study population although as you state in the paper it may not be a true national representation. Why limit the study population to 400?

The following graph presents details of precision around various assumptions in terms of observed proportion for a sample of 400. Specifically, it depicts the relationship between the proportion of respondents that would be found for a given question (e.g., the proportion of physicians who would recommend a same-day office visit for a 0-2 month
old with a fever of 38c) and the precision (based on the half-width of the confidence interval) that would be obtained with a sample size of 400 physicians. The diamonds in the graph indicate data points calculated using the formula and a curve has been drawn through the data points. Given the expected proportions, a target sample of 400 responders resulted in an appropriate level of precision to address the study objectives.

I think that the most important message in the manuscript is how fever is treated differently after vaccinations. Has this been studied before? Management of fever in young children vs older has been extensively studied. Is the new thing here management of fever after vaccination?

Yes, the new contribution of the manuscript is that we are evaluating the attitude of pediatricians regarding fever after vaccination. This was mentioned in the background section.

Abstract - The abstract should have a specific objective statement unless this is specific journal requirements.

The objective was mentioned in the background section of the abstract.

Background - 3rd paragraph, 4th sentence should start with beliefs. The last sentence in the 3rd paragraph is awkward to me. What does predicted mean?
The background needs more. What has been done before regarding pediatric perceptions and what does this study add? I wonder if the last sentence should be in the discussion section.

We edited the word "beliefs" as suggested. 
We changed the word "predicted" to "practiced" 
We added the reference of Chiappini et al 2009 in the background section.

Methods - How was the random sample drawn - computer generated, random number table?

We added a statement in the "sampling and data collection" section on page 6 to explain that the sample was randomly computer generated.

Why 400? GEE makes sense here. Do you have to do any other adjustments to the analysis because it was a national survey? Otherwise this section is well written.

We explained previously why the sample was limited to 400 based on the precision estimation. We did not have to do any adjustments.

Results - Be careful not to re-state data that is in the tables. The results section should just state findings without interpretation. In the section "Predictors of recommendation for fever management" the second sentence is a summary statement and should be in the discussion.

We do not believe that the second sentence is a summary statement since we are listing the results of the regression as well.

It is very interesting that respondents in group practice were less likely to recommend hospital admission or ER. Why do you think that is? In the section on influence of practicing guidelines I wonder if there are differences between those who state they follow guidelines vs. those who do not. This would be very interesting. Is the sample too small - about 40 stating they don't use guidelines?

Actually not all respondents in group practice were less likely to recommend hospital admission or ER. Pediatricians who are practicing in solo or in group office were less likely to recommend hospital admission or ER than those who are practicing in an HMO setting. Perhaps those who are in an HMO setting are more comfortable to send patients to a hospital or the ER since these facilities are usually within the same system.

We did not evaluate whether those who follow the guidelines have a different behavior than those who do not. This was not the scope of the paper and the study was not designed to look at this difference. We were mostly focused on the difference in the
pediatrician's behavior based on whether the child was vaccinated. Yes, about 40 respondents stated that they do not use the guidelines.

Discussion - for the most part this is well written. What is groundbreaking about your findings? Is it the management of fever after vaccinations? If so this should be the emphasis of the paper.

Yes, the main result is that the management of fever depends on several factors including the vaccination status. This was emphasized in the discussion section as well as the conclusion.

Conclusion - The last sentence - What do you mean by these results may be valuable when estimating burden of managing fever? Its a strong statement that needs more clarification.

The economic burden of managing fever will depend on the pediatricians recommendation for managing fever. We did not want to discuss this issue in the discussion because this was not the scope of this paper. However it is important to note that the results of this survey may be useful to estimate the economic burden of fever.

Table 2 - At the bottom of table you should state what's included in the multivariable model.

The variables are listed in the table itself.