

# EVIDENCIAS EN PEDIATRÍA

Toma de decisiones clínicas basadas en las mejores pruebas científicas

[www.evidenciasenpediatria.es](http://www.evidenciasenpediatria.es)

## Critically Appraised Articles

### Prophylactic administration of acetaminophen in childhood vaccination is still not recommended

De Lucas García N<sup>1</sup>, Aparicio Rodrigo M<sup>2</sup>

<sup>1</sup>SAMUR-Protección Civil. Madrid. Spain.

<sup>2</sup>CS Entrevías. Department of Paediatrics. School of Medicine. Universidad Complutense de Madrid. Madrid. Spain.

Correspondence: Nieves de Lucas García, [delucasn@gmail.com](mailto:delucasn@gmail.com)

---

**English key words:** immunogenicity, vaccine, paracetamol, pentavalent vaccine, prophylactic, vaccine.

**Spanish key words:** inmunogenicidad vacunal, paracetamol, vacuna pentavalente, profiláctico, vacuna.

**Reception date:** September 25, 2017 • **Acceptance date:** September 28, 2017

**Publication date:** October 4, 2017

---

Evid Pediatr. 2017;13:33.

#### HOW TO CITE THIS ARTICLE

De Lucas García N, Aparicio Rodrigo M. Por el momento se sigue desaconsejando la administración profiláctica de paracetamol en la vacunación infantil. Evid Pediatr. 2017;13:33.

To receive Evidencias en Pediatría in your e-mail you must sign up for our newsletter at  
<http://www.evidenciasenpediatria.es>

---

This article is available at <http://www.evidenciasenpediatria.es/EnlaceArticulo?ref=2017;13:33>

©2005-17 • ISSN: 1885-7388

# Prophylactic administration of acetaminophen in childhood vaccination is still not recommended

De Lucas García N<sup>1</sup>, Aparicio Rodrigo M<sup>2</sup>

<sup>1</sup>SAMUR-Protección Civil. Madrid. Spain.

<sup>2</sup>CS Entrevías. Department of Paediatrics. School of Medicine. Universidad Complutense de Madrid. Madrid. Spain.

Correspondence: Nieves de Lucas García, delucasn@gmail.com

**Artículo original:** Sil A, Ravi MD, Patnaik BN, Dhingra MS, Dupuy M, Gandhi DJ, et al. Effect of prophylactic or therapeutic administration of paracetamol on immune response to DTWP-HepB-Hib combination vaccine in Indian infants. *Vaccine*. 2017;35:2999-3006.

## Abstract

**Authors' conclusions:** the study found no evidence that paracetamol usage either as prophylactic or for treatment impact immunological responses to DTWP-HepB-Hib combination vaccine

**Reviewers' commentary:** the methodological deficiencies of this study do not allow to make any change in the current clinical practice, which discourages the prophylactic administration of acetaminophen in childhood vaccination.

**Key words:** immunogenicity, vaccine, paracetamol, pentavalent vaccine, prophylactic, vaccine.

**Por el momento se sigue desaconsejando la administración profiláctica de paracetamol en la vacunación infantil**

## Resumen

**Conclusiones de los autores del estudio:** no se encontraron evidencias de que el paracetamol, administrado tanto de forma profiláctica como terapéutica, tenga un impacto sobre la respuesta inmunológica a la vacuna pentavalente DTPc-HepB-Hib.

**Comentario de los revisores:** las limitaciones metodológicas de este estudio no permiten realizar ningún cambio en la práctica clínica actual, que desaconseja la administración profiláctica del paracetamol en la vacunación infantil.

**Palabras clave:** inmunogenicidad vacunal, paracetamol, vacuna pentavalente, profiláctico, vacuna.

## STRUCTURED ABSTRACT

**Objective:** to assess the effect of the administration of paracetamol (prophylactic [PP] or therapeutic [TP]) on the immune response to the pentavalent vaccine (diphtheria, tetanus, cellular pertussis, hepatitis B, *Haemophilus influenzae*) (PV) in infants.

**Design:** cohort study performed by means of a *post hoc* analysis of the data of a multicentre (11 study sites) randomised single-blind controlled clinical trial designed to compare two pentavalent vaccines (the vaccine manufactured by Sanofi Pasteur versus a locally-licensed vaccine manufactured in India).

**Setting:** India.

**Study population:** 1085 infants aged 6 to 8 weeks. Exclusion criteria: born at less than 37 weeks' gestation, chronic disease, receipt of any other vaccine except oral polio, birth

dose of hepatitis B or the bacillus Calmette-Guérin (BCG) vaccines.

**Intervention:** the authors analysed the immune response that followed administration of three doses of two different formulations of PV (at 6-8 weeks, 10-12 weeks, 14-16 weeks) and its correlation to the administration of paracetamol (PP or TP) or lack thereof.

**Outcome measurement:** levels of antibodies (seroprotection) against diphtheria ( $\geq 0.01$  IU/ml), tetanus ( $\geq 0.01$  IU/ml) and *Haemophilus influenzae* ( $\geq 0.15$  µg/ml) and two types of seroresponse for antibodies against pertussis (if initially seropositive: increase from pre-vaccination titre; if seronegative: 4-fold titre rise) and hepatitis B ( $\geq 10$  IU/ml before and after administration of PV).

**Main results:** the analysis included 928 patients (85%). It found differences in the immune response of patients with paracetamol (both PP and TP) and without paracetamol in the

analysis of the two vaccines (pooled and separate) against pertussis, *Haemophilus influenzae* and hepatitis B. It found a lower level of antibodies against tetanus (pooled results) in patients with PP versus patients without paracetamol, although there were no differences between the PP group and any of the other two groups. The levels of antibodies against diphtheria in infants with PP that received the locally-licensed vaccine were lower than those of children without paracetamol in the same group, there were no differences between the PP and the other two groups in this vaccine group or in the pooled analysis for both vaccines. The sero-response to the vaccine against pertussis was similar in every group (without paracetamol: 63.6%; 95% confidence interval [95 CI]: 58.8 to 68.3]; PP: 69% [95 CI: 56.9 to 79.5]; TP: 66% [95 CI: 61.4 to 70.4]).

**Conclusion:** the data suggested that paracetamol given for either prophylaxis or treatment of vaccine reactions after administration of the PV does not impact the immune response to the vaccine. The observed differences were minimal and seemed to be of no clinical relevance.

**Conflicts of interest:** ten of the 21 authors, including those listed first and last, were employees of the manufacturer or the investigational vaccine (Sanofi Pasteur). The rest of the authors received research grants from the Sanofi Pasteur laboratories.

**Funding source:** the Sanofi Pasteur pharmaceutical company, which owns the trademark for the investigational vaccine.

## COMMENTARY

**Justification:** one of the most frequent adverse effects that follow vaccination in children is fever. Post-vaccine administration of paracetamol, especially for prophylactic purposes, could interfere with the immune response to vaccination.<sup>1,2</sup>

**Validity or scientific rigour:** this is a *post hoc* analysis of the data of a clinical trial, so it did not follow a pre-established study design and the necessary sample size to address the research question was not calculated. It analysed 928 infants of the 1085 included in the original clinical trial<sup>3</sup> (with losses of 15%), whose purpose was not to analyse the effects of paracetamol, so that data collection on this factor could have been less rigorous, and it is quite possible that relevant variables and potential confounding factors were not included. Three groups were compared: infants that did not receive paracetamol, infants that received PP and infants that received TP. The authors did not state how they obtained the data on the use of paracetamol. We do not know whether the characteristics of the infants included in each of the three groups were similar. There were no documented indications for the prophylactic or therapeutic use of paracetamol (fever, dose, interval) either in this study or in the original clinical trial, nor in the trial information recorded in the registry.<sup>4</sup> The authors performed a descriptive analysis with 95 CIs, specifying the cases in which the intervals did not overlap; however, some of

the groups under comparison seemed small (PP) and this small sample size may have contributed to the disparity in the results, which do not seem to have a plausible clinical explanation (increase in antibody levels in some analyses with decrease in others). Since multiple comparisons were performed, it would have been advisable to set a higher level of confidence for the estimation of the intervals. Of the 21 authors, 10 (including the authors listed first, third, fourth, fifth and last) were employed by the manufacturer that funded the study, although there is no clear conflict of interests in the *ad hoc* study. The problems with internal validity limit the external validity of the study. In any case, the fact that the study was conducted in children that received the whole-cell pertussis vaccine precludes the extrapolation of its results to children vaccinated with the acellular vaccine, which causes fewer adverse events.

**Clinical relevance:** this study did not find changes in the post-vaccination levels of antibodies associated with the use of paracetamol. The pooled analysis found significant differences in only two of the 24 compared intervals found significant differences, neither with the response percentage, only for the TP group and with an opposed effect direction. The results of this study differ from those of previous studies<sup>1,2</sup> that have more appropriate designs and which found that the prophylactic administration of paracetamol interfered with the antibody response to vaccination.

**Applicability to clinical practice:** the methodology of the article does not support making any changes to current clinical practice, in which the prophylactic use of paracetamol is recommended against.

**Conflicts of interest:** the authors of the commentary have no conflicts of interest to declare.

## REFERENCES

1. Prymula R, Siegrist CA, Chlibek R, Zemlickova H, Vackova M, Smetana J, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 2009;374:339-50.
2. Doedée AM, Boland GJ, Pennings JL, de Klerk A, Berbers GA, Van der Klis FR, et al. Effects of prophylactic and therapeutic paracetamol treatment during vaccination on hepatitis B antibody levels in adults: two open-label, randomized controlled trials. *PLoS One*. 2014;9:e98175.
3. Gandhi DJ, Dhaded SM, Ravi MD, Dubey AP, Kundu R, Lalwani SK. Safety, immune lot-to-lot consistency and non-inferiority of a fully liquid pentavalent DTwP-HepB-Hib vaccine in healthy Indian toddlers and infants. *Hum Vaccines Immunother*. 2016;12:946-54.
4. CTRI Trial Data In: Clinical Trials Registry (India) [online] [accessed 28/09/2017]. Available at: [http://www.ctri.nic.in/Clinicaltrials/pdf\\_generate.php?trialid=5063&EncHid=&modid=&compid=%27,%275063det%27](http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=5063&EncHid=&modid=&compid=%27,%275063det%27)