

## Ch11.05. Acetaminophen with Vaccines (With thanks to Dr. Andrea Wickremasinghe)

Babies often get fevers from vaccines, and their caretakers often give them acetaminophen (Tylenol®, called paracetamol in Europe) to try to prevent (and treat) these fevers. Prymula et al.[1] reported a randomized trial of the effect of prophylactic acetaminophen on fever reduction and vaccine antibody responses in infants receiving immunizations. They found that 94/226 infants in the acetaminophen group (41.6%) developed fever  $\geq 38^\circ\text{C}$ , compared with 154/233 control infants (66.1%).

The Methods section states:

"The primary objectives were reached if the lower limit of the standardised asymptotic 95% CI for the difference between groups in terms of percentage of participants with rectal temperature  $38^\circ\text{C}$  or greater after at least one vaccine dose was above 0%,"

and the results state,

"The primary objective... [was] met, since the lower limit of the 95% CI around the group difference was greater than 0 (...difference 24.5% [95% CI 15.5, 33.1%])."

a.) Indicate whether each of the following statements is true or false and briefly explain your answer:

i.) Based on the 95% CI above, the authors could reject the null hypothesis of no difference between groups at  $\alpha = 0.05$ .

**TRUE. We reject the null hypothesis if  $P < \alpha$ , and in fact  $P < 0.001$ .**

ii.) The *lower* limit of the 95% CI for the Number Needed to Treat (to prevent one infant from developing a temperature  $\geq 38^\circ\text{C}$ ) is about 3.

**TRUE, the lower limit is 1/33.1%, very close to 3.**

iii.) If we were to repeat this study 100 times, we would expect that in 95% of those studies the point estimate for the difference in proportions of infants with temperatures  $\geq 38^\circ\text{C}$  would be between 15.5% and 33.1%.

**FALSE, if we were to repeat the study 100 times, we would expect the 95% CI of (on average) 95 of the studies to include the true value. The statement above implies we know something about the posterior probability that the 95% CI includes the true value, and we do not.**

b) For most vaccines, there were no statistically significant differences in the proportions of children in the two groups with protective antibody levels. For example, for Serotype 1 pneumococcus, 202/207 children treated with paracetamol had protective antibody levels (97.6%), compared with 224/226 untreated children (99.1%).

Using the shortcut described in Chapter 11, what is the lower limit of the 95% confidence interval for the proportion with protective antibody levels for Serotype 1 in the untreated children?

**If we consider treatment failures, with an observed proportion of 2/226, using the rule of 3,5,7,9, 10 for numerators of 0,1,2,3,4, the upper limit of the 95% CI for this numerator of 2 is about  $7/226 = 3.1\%$ . So the lower limit of the 95% CI should be about  $1 - 3.1\% = 96.9\%$ . (The actual exact lower limit of the 95% CI is 96.8%.)**

c) The concerning result of this study was that the paracetamol-treated infants had statistically significantly lower geometric mean antibody titers to almost all of the antigens in the vaccines. The authors concluded that, "...prophylactic administration of antipyretic drugs at the time of vaccination should not be routinely recommended since antibody responses to several vaccine antigens were reduced." Do you agree with this conclusion? What additional information would you want to in order to decide?

**TBN: I tend to agree, because I am sort of a minimalist and don't like acetaminophen anyway because of concerns about prenatal and early postnatal exposure to it causing asthma.[2, 3] Some things we would want to know more about are: 1) how severe the febrile reactions were (hardly any were over 39° C); 2) safety and efficacy of alternatives to "routine" acetaminophen use (e.g., acetaminophen as needed or ibuprofen prophylactically or as needed) and the clinical significance of the lower geometric mean antibody titers. Ideally, we'd want a large double-blind RCT powered to look at vaccine-preventable disease incidence, (and rare side effects). In the absence of that, I'd want to know how good the data are about "protective" levels of antibody.**

**MAK: I am less of a minimalist. I don't mind pre-treating kids with acetaminophen before vaccines, because they sometimes end up in the ED when they do develop a fever and/or fussiness after a shot. It is always better to talk to the parents and say, "He may get a fever that you can treat with acetaminophen *and not take him to the emergency department.* Alternatively, I can give him acetaminophen now, but there is some (weak) evidence that this decreases the shot's effectiveness." It's weak evidence because both groups got protective levels of antibodies and this statistically significant difference in geometric mean antibody levels may have no clinical significance.**

## 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(9698):1339-50.
2. Shaheen SO. Acetaminophen and childhood asthma: pill-popping at our peril? *J Allergy Clin Immunol*. 2015;135(2):449-50.

3. Magnus MC, Karlstad O, Haberg SE, Nafstad P, Davey Smith G, Nystad W. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study. *Int J Epidemiol.* 2016;45(2):512-22.