



Q/Do prophylactic antipyretics reduce vaccination-associated symptoms in children?

EVIDENCE-BASED ANSWER

A | YES for acetaminophen, not so much for ibuprofen. Prophylactic acetaminophen reduces the odds of febrile reactions in the first 48 hours after vaccination by 40% to 65% and pain of all grades by 36% to 43%. In contrast, prophylactic ibuprofen reduces pain of all grades by 34% only after primary vaccination and doesn't alter pain after boosters. Nor does it alter early febrile reactions (strength of

recommendation [SOR]: **B**, meta-analysis of randomized clinical trials [RCTs] with moderate-to-high risk of bias).

Prophylactic administration of acetaminophen or ibuprofen is associated with a reduction in antibody response to the primary vaccine series and to influenza vaccine, but antibody responses still achieve seroprotective levels (SOR: **C**, bench research).

Evidence summary

A systematic review of 13 RCTs (5077 patients) compared the effects of a prophylactic antipyretic (acetaminophen or ibuprofen, doses and schedules not described) with placebo in healthy children 6 years or younger undergoing routine childhood immunizations.¹ Trials examined various schedules and combinations of vaccines. Researchers defined febrile reactions as a temperature of 38°C or higher and categorized pain as: none, mild (reaction to touch over vaccine site), moderate (protesting to limb movement), or severe (resisting limb movement).

Acetaminophen works better than ibuprofen for both fever and pain

Acetaminophen prophylaxis resulted in fewer febrile reactions in the first 24 to 48 hours after vaccine administration than placebo following both primary (odds ratio [OR] = 0.35; 95% confidence interval [CI], 0.26-0.48) and booster vaccinations (OR = 0.60; 95% CI, 0.39-0.93). Acetaminophen also reduced pain of all grades (primary vaccination: OR = 0.57; 95% CI, 0.47-0.7; booster

vaccination: OR = 0.64; 95% CI, 0.48-0.84).

In contrast, ibuprofen prophylaxis had no effect on early febrile reactions for either primary or booster vaccinations. It reduced pain of all grades after primary vaccination (OR = 0.66; 95% CI, 0.49-0.88) but not after boosters (OR = 1.03; 95% CI, 0.59-1.81).

Reduced antibody response doesn't affect seroprotective levels

Acetaminophen also generally reduced the antibody response compared with placebo (assessed using the geometric mean concentration [GMC], a statistical technique for comparing values that change logarithmically).¹ GMC results are difficult to interpret clinically, however, and they differed by vaccine, antigen, and primary or booster vaccination status.

Nevertheless, patients mounted seroprotective antibody levels with or without acetaminophen prophylaxis, and the nasopharyngeal carriage rates of *Streptococcus pneumoniae* and *Haemophilus influenzae* didn't change. Researchers didn't publish the antibody responses to ibuprofen, nor did they track actual infection rates.

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➤ Prophylactic acetaminophen reduces the odds of febrile reactions in the first 48 hours after vaccination by 40% to 65% and pain of all grades by 36% to 43%.

How do antipyretics work with newer combination vaccines?

A subsequent trial evaluated the immune response in 908 children receiving newer combination vaccines (DTaP/HBV/IPV/Hib and PCV13) who were randomized to 5 groups: acetaminophen 15 mg/kg at vaccination and 6 to 8 hours later; acetaminophen 15 mg/kg starting 6 to 8 hours after vaccination with a second dose 6 to 8 hours later; ibuprofen 10 mg/kg/dose at vaccination with a second dose 6 to 8 hours later; ibuprofen 10 mg/kg starting 6 to 8 hours after vaccination with a second dose 6 to 8 hours later; and placebo.²

Patients received age-appropriate vaccination and their assigned antipyretic (or placebo) at 2, 3, 4 and 12 months of age. Researchers measured the immune response at 5 and 13 months of age.

Overall, 5% to 10% of the prophylaxis group had fever on Day 1 or 2 after vaccination, compared with 10% to 20% of the placebo group (no *P* value given). Antipyretic use produced lower antibody GMC responses for antipertussis and antitetanus vaccines at 5 months but not at 13 months. Patients achieved the prespecified effective antibody levels at both 5 and 13 months, regardless of intervention.

Antipyretics don't affect immune response with inactivated flu vaccine

A 2017 RCT investigated the effect of either prophylactic acetaminophen (15 mg/kg every 4 to 6 hours for 24 hours) or ibuprofen (10 mg/kg every 4 to 6 hours for 24 hours) on immune response in children receiving inactivated influenza vaccine.³ Researchers randomized 142 children into 3 treatment groups (acetaminophen, 59 children; ibuprofen, 24 children; placebo, 59 children). They defined seroconversion as a hemagglutinin

inhibition assay titer of 1:40 postvaccination (if baseline titer was less than 1:10) or a 4-fold rise (if the baseline titer was \geq 1:10).

All interventions resulted in similar seroconversion rates for all A or B influenza strains investigated. Vaccine protection-level responses ranged from 9% for B/Phuket to 100% for A/Switzerland. The trial didn't report febrile reactions or infection rates.

Recommendations

In 2017, the Advisory Committee on Immunization Practices (ACIP) issued guidelines generally discouraging the use of antipyretics at the time of vaccination, but allowing their use later for local discomfort or fever that might arise after vaccination. The guidelines also noted that antipyretics at the time of vaccination didn't reduce the risk of febrile seizures.⁴

Editor's takeaway

Although ACIP doesn't encourage giving antipyretics with vaccines, moderate-quality evidence suggests that prophylactic acetaminophen reduces fever and pain after immunizations by a reasonable amount without an apparent clinical downside. **JFP**

References

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4. Kroger AT, Duchin J, Vázquez M. General Best Practice Guidelines for Immunization. *Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2017.