Prophylactic antipyretics for prevention of febrile seizures following vaccination

Nicholas Monfries MD Ran D. Goldman MD FRCPC

Abstract

Question Parents of a 12-month-old boy are bringing their son in to my family practice clinic for his well-baby visit. As the infant is due for his 12-month vaccine series, the parents are concerned after hearing about the association between certain vaccinations and an increased risk of febrile seizures, and are wondering if they should administer prophylactic antipyretics to decrease the risk of febrile seizure. What vaccinations are associated with increased risk of febrile seizure, and is there evidence supporting prophylactic administration of antipyretics to prevent febrile seizures?

Answer Vaccinations associated with increased risk of febrile seizure include the following: the measles-mumps-rubella vaccine; the measles-mumps-rubella-varicella vaccine; the combined diphtheria, tetanus, acellular pertussis, polio, and *Haemophilus influenzae* type b vaccine; the whole-cell pertussis vaccine; the 7-valent pneumococcal conjugate vaccine; and concomitant administration of the trivalent inactivated influenza vaccine with either the 7-valent pneumococcal conjugate vaccine or the diphtheria, tetanus, and acellular pertussis vaccine. Despite being a higher-risk group, children receiving these vaccinations should not receive prophylactic antipyretics, as no statistically significant reduction in the rate of febrile seizures has been documented, and prophylactic antipyretic use potentially decreases the immune response to certain vaccines.

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Fever is one of the most common adverse events following immunization, affecting 1% to 10% of children in the United States, with the incidence varying depending on the type of vaccination.[1]

Febrile seizure is the most common convulsive event presenting in children younger than 5 years of age, occurring in 2% to 5% of children.[2] *Febrile seizure* is a misnomer because while the episodes of seizures are likely associated with fever, they are not necessarily caused by the high temperature, and they have a distinct physiology, different than nonconvulsive febrile episodes.[3] Febrile seizures are simple or complex.[4] A simple febrile seizure is generalized, lasts less than 15 minutes, and occurs only once in a 24-hour period.[5]

A family history of febrile seizure,[4] viral infections such as influenza A and human herpesvirus 6,[5,6] and certain vaccinations[7-12] are considered risk factors for febrile seizures. Febrile seizures recur in an estimated 23% to 43% of all children who experience a first-time episode.[13]

Vaccinations and febrile seizures

Since the establishment of the Vaccine Safety Datalink project, initiated by the Centers for Disease Control and Prevention in 1990 to study adverse events after childhood immunizations, an association was reported between certain vaccinations and febrile seizures.[8] Barlow et al found a statistically significant risk of febrile seizure 8 to 14 days after administration of the measles-mumps-rubella (MMR) vaccine (relative risk [RR] of 2.83, 95% CI 1.44 to 5.55).[8] The whole-cell pertussis vaccine used in isolation was also found to be associated with an increased risk of febrile seizure on the day of administration (RR = 5.70, 95% CI 1.98 to 16.42) but not during later time periods.[8]

Furthermore, some combined vaccinations have a higher risk of febrile seizure than their separately administered vaccine components do. Using data from the Vaccine Safety Datalink, Klein et al found a 2-fold increase in risk of febrile seizure with the combined measles-mumps-rubella-varicella vaccine compared with the separately administered MMR and varicella vaccines; however, the overall risk was small (equating to an additional 4.3 febrile seizures per 10 000 doses [95% CI 2.6 to 5.6]).[9] Among a similar age demographic in Canada, adjusted relative risk of febrile seizure for being vaccinated approximately doubled with the combination measles-mumps-rubella-varicella vaccine (RR = 6.57, 95% CI 4.77 to 9.05), compared with the separately

administered MMR and varicella vaccines (RR=3.30, 95% CI 2.40 to 4.52).[10] In a population-based cohort study of children born in Denmark in 2003 to 2008, the combined diphtheria, tetanus, acellular pertussis, polio, and *Haemophilus influenzae* type b vaccine increased the risk of febrile seizure for infants on day 1 and day 2 after administration, with hazard ratios of 6.02 (95% CI 2.86 to 12.65) and 3.94 (95% CI 2.18 to 7.10), respectively.[11]

In a recent study, Duffy et al investigated the association of febrile seizure risk with the trivalent inactivated influenza vaccine, a pneumococcal conjugate vaccine (PCV), and a diphtheria, tetanus, and acellular pertussis (DTaP)–containing vaccine, used alone and in combination, among children 6 to 23 months of age during the 2006 to 2011 influenza seasons. The authors reported an increased risk of febrile seizure when the 7-valent PCV was administered alone (RR=1.98, 95% CI 1.00 to 3.91), as well as when the trivalent inactivated influenza vaccine was concomitantly administered with the 7-valent PCV (RR=3.50, 95% CI 1.13 to 10.85) or with a DTaP-containing vaccine (RR=3.50, 95% CI 1.52 to 8.07).[12]

It is clear from the evidence that certain vaccines and vaccine combinations independently increase a child's risk of developing a febrile seizure. While the increased risk of febrile seizure following vaccination is small, witnessing a febrile seizure can be a frightening experience for parents and caregivers. In hopes of preventing seizures, as well as caring for pain[14] and fever, health care providers and parents routinely administer antipyretics around the time of vaccination.

Antipyretics and febrile seizures

Based on past assumption that there was a causal relationship between fever and febrile seizures, investigators hypothesized that antipyretic use might prevent febrile seizures.[15] One trial compared the administration of prophylactic acetaminophen (15 to 20 mg/kg every 4 hours) with the sporadic administration of acetaminophen (15 to 20 mg/kg only for temperatures higher than 37.9°C) in children aged 6 to 60 months presenting to hospital with a simple febrile seizure, and found no statistically significant difference in the rate of febrile seizures (7.5% and 9.8% recurrence, respectively). Similarly, a 2-phased randomized controlled trial concluded that acetaminophen (10 mg/kg up to 4 times per day for temperatures higher than 40°C) did not prevent febrile seizure recurrence in children. The recurrence rate for each group (placebo and placebo, placebo and acetaminophen, diazepam and acetaminophen, and diazepam and diazepam) was 8.2%, 5.2%, 9.9%, and 11.5%, respectively.[16] Therefore, the evidence suggests that acetaminophen is not effective at preventing febrile seizure recurrence.

The efficacy of ibuprofen in reducing febrile seizure recurrence has also been evaluated. Van Stuijvenberg et al reported on a group of 230 children (12 to 48 months old) who had had a febrile seizure and had at least 1 additional risk factor for recurrence (including a family history of febrile seizures, a multiple-type febrile seizure, a temperature of less than 40°C at initial seizure onset, and recurrent febrile seizures). Each child received ibuprofen (5 mg/kg per dose) or a placebo every 6 hours at the first sign of fever (temperature higher than 38.5°C) until the child was afebrile for 24 hours. Using an intention-to-treat analysis, the authors did not find a statistically significant difference between the 2 groups, with an estimated 2-year probability of recurrence of 32% for the ibuprofen group and 39% for the placebo group (P=.7).[17]

Another group of children (aged 4 to 48 months) presenting to 5 hospitals in Finland with febrile seizure were randomized to receive 1.5 mg/kg of rectal diclofenac (a nonsteroidal anti-inflammatory drug) or a placebo, followed by either acetaminophen (15 mg/kg), ibuprofen (10 mg/kg), or a placebo up to 4 times per day as long as their temperature was higher than 38°C. The seizure recurrence rate was nearly identical at the 2-year follow-up: 23.4% for the treatment group and 23.5% for the placebo group (difference of 0.2; 95% CI -12.8 to 17.6; P=.99), suggesting no value in administration of antipyretics.[18]

Antipyretics and vaccinations

While there is no published literature, to our knowledge, that specifically addresses prophylactic antipyretic use to reduce the risk of febrile seizure in the population of children receiving vaccinations, there might be some risk of decreased immunogenicity.[19] A systematic review investigating the effect of prophylactic antipyretic use and postvaccination adverse events in children younger than age 6 revealed a statistically significant decrease in postvaccination antibody levels in patients who received acetaminophen alone or in combination with ibuprofen at the time of vaccination with a diphtheria-containing vaccine (DTaP or whole-cell pertussis), administered alone or co-administered with a pneumococcal-containing vaccine and *Haemophilus influenzae* type b vaccine. However, these findings are based on only 2 published heterogeneous studies and are of unclear clinical significance, given the lack of established guidelines on the necessary antibody levels that will be protective for the vaccines studied.[20] More research is needed to further elucidate the effect of prophylactic antipyretics on the immune response to vaccines, specifically exploring how the diminished immune response affects the effectiveness of the vaccine at a population level.

Although current literature does not support antipyretic use for reducing the risk of febrile seizure following vaccination, the age at which a child receives a vaccine might be associated with the risk of postvaccination febrile seizure. Rowhani-Rahbar et al reported that,

in a group of children aged 12 to 23 months, there was a statistically significant decrease in the incidence of febrile seizure in children who received their first dose of MMR vaccine between 12 and 15 months of age, compared with those children who received the vaccine at an older age.[21] Therefore, it appears that prudent timing of MMR vaccination is the only known factor that decreases the rate of febrile seizure recurrence following vaccination.

Conclusion

Febrile seizures are common in children. It is typically a benign condition with favourable long-term outcomes. While an association between certain vaccines and febrile seizures exists, the risk is small and outweighs the risk of not being vaccinated. Current evidence does not suggest benefit to providing prophylactic antipyretics, especially in face of potential lack of immunogenicity.

Competing interests
None declared

Correspondence
Dr Ran D. Goldman; e-mail **rgoldman@cw.bc.ca**

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