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# Best Practice for Treatment of Vaccination Side-effects with Antipyretic and Analgesic Medications

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Best Practice for Treatment of Vaccination Side-effects with  
Antipyretic and Analgesic Medications

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An evidence based scholarly paper submitted to the faculty of  
Brigham Young University  
in partial fulfillment of the requirements for the degree of Masters of  
Science

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## ABSTRACT

Best Practice for Treatment of Vaccination Side-effects with  
Antipyretic and Analgesic Medications

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Nurse Practitioners (NPs) are on the frontlines providing parental education regarding vaccines. While there are several reasons for vaccine hesitancy, the potential side-effects of vaccine administration, such as pain and/or elevated temperature, are often cited as a parental concern. According to research, prophylactic administration of an antipyretic/analgesic medication, such as acetaminophen, reduces vaccine side-effects when administered prior to or at the time of vaccination. Additionally, the evidence that prophylactic administration of antipyretic/analgesic medication decreases antibody response to vaccinations is insufficient at this time. Thus, NPs should reassure parents that an antipyretic/analgesic medication can be administered prior to or at the time of vaccination to prevent or reduce side-effects, which may then reduce vaccine hesitancy among parents.

Keywords: acetaminophen, antipyretic, analgesic, immunization, prophylactic, vaccine

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## TABLE OF CONTENTS

Abstract.....	ii
Acknowledgments.....	iii
Introduction.....	1
Methods.....	2
Results.....	2
Local Vaccine Reactions.....	3
Redness and Swelling .....	3
Pain .....	4
Systemic Vaccine Reactions .....	4
Elevated Temperature .....	4
Administration Scheduled.....	4
Administration As-needed .....	5
Administration in Series .....	6
Fussiness .....	6
Sleep.....	7
Antibody Response .....	7
Discussion.....	8
Implications for Nurse Practitioners .....	9
Conclusion .....	10
References.....	12

## Best Practice for Treatment of Vaccination Side-effects with Antipyretic and Analgesic Medications

Well-child examinations, common reasons for clinic visits with nurse practitioners (NPs), comprise 50-70% of the total patient visits during an average clinic day (Pedulla, 2012). The American Academy of Pediatrics (AAP) (2015) recommends the administration of vaccinations during most routine well-child examinations. According to the Centers for Disease Control and Prevention (CDC) (2016), the majority of childhood vaccinations are administered during the first 18 months of life. However, sometimes infants and young children experience common side-effects to vaccines such as elevated temperature, tenderness and/or swelling at the injection site (Pedulla, 2012). In an effort to minimize potential and bothersome vaccine side-effects, parents and NPs commonly administer antipyretic/analgesic medications to infants and young children prior to or at the time of routine vaccinations (Honne & Fischer, 2010).

While antipyretic/analgesic medications, such as ibuprofen, acetaminophen (available in the United States [US]), and paracetamol (available outside the US), are generally safe for use in infants and young children, administering these medications prophylactically for vaccine-related side-effects is sometimes surrounded by controversy (Pedulla, 2012). One notable concern is that antipyretic/analgesic medication administration prior to or at the time of vaccination can negatively affect the child's ability to produce an effective immune response to vaccines (Prymula et al., 2009). Conversely, antipyretic/analgesic medications also effectively treat common vaccination side-effects, such as elevated temperature and discomfort. As vaccine champions, NPs should provide evidence-based education to parents regarding the potential benefits and risks of antipyretic/analgesic medication and vaccination. Therefore, the purposes of this article are to: 1) review the literature regarding the prophylactic use of

antipyretic/analgesic medications prior to or at the time of vaccination administration; and 2) make a clinical recommendation for the NP regarding best practice.

### **Methods**

CINAHL, Medline, and the Cochrane Library were searched to identify articles examining prophylactic antipyretic/analgesic medication use for vaccination administration. Additionally, select websites were reviewed, including the CDC and the US Department of Health and Human Services websites. Search terms included *acetaminophen, ibuprofen, paracetamol, antipyretic, prophylactic, immunization, vaccine, fever, febrile, adverse side-effects or reactions, pain, swelling, irritability, fussiness, and antibody*. Only randomized control trials (RCTs) published in the English-language were included for review. Articles were included if published since 1987, which was the year of the first published RCT on this topic. Because the focus of this literature review was on antipyretic/analgesic medication use in infants and children before, at the time of, or after vaccination administration, articles regarding antipyretic/analgesic medication use for adolescent and adult vaccinations were excluded.

### **Results**

Thirteen articles met inclusion criteria. While all 13 studies included research regarding the effect of antipyretic/analgesic medications on vaccine-related side-effects, the type of antipyretic/analgesic medication differed from study to study as well as the type of vaccine administered. Additionally, some researchers evaluated the effect of antipyretic/analgesic medications on the patient's ability to produce a healthy antibody response after vaccination.

Three main outcomes were measured in the 13 studies, namely, the effect of antipyretic/analgesic medications on local vaccine reactions, systemic vaccine reactions, and antibody response. Nine studies focused on the antipyretic/analgesic medication effect on local

vaccine reactions, specifically vaccine site redness, swelling, and pain (Dhingra & Mishra, 2011; Díez-Domingo et al., 1998; Hayat, Khan, & Hayat, 2011; Ipp et al., 1987; Jackson et al., 2006; Lewis et al., 1988; Prymula et al., 2009; Rose et al., 2013; Yalçin, Gümüş, & Yurdakök, 2008). Eleven studies evaluated the effect of antipyretic/analgesic medications on systemic vaccine reactions, such as elevated temperature, fussiness, and sleep duration (Dhingra & Mishra, 2011; Díez-Domingo et al., 1998; Franck, Gay, Lynch, & Lee, 2011; Hayat et al., 2011; Ipp et al., 1987; Jackson et al., 2011; Lewis et al., 1988; Prymula et al., 2009; Rose et al., 2013; Uhari, Hietala, & Vilajanen, 1988; Yalçin et al., 2008). Researchers also measured the effect of antipyretic/analgesic medications on antibody response in three studies (Prymula, Habib, François, Borys, & Schuerman, 2013; & Prymula et al., 2009; Uhari et al., 1988).

### **Local Vaccine Reactions**

**Redness and swelling.** Eight RCTs addressed the relationship between redness and swelling at the vaccination site and antipyretic/analgesic medication administration (Díez-Domingo et al., 1998; Hayat et al., 2011; Ipp et al., 1987; Jackson et al., 2006; Lewis et al., 1988; Prymula et al., 2009; Rose et al., 2013; Yalçin et al., 2008). In six RCTs, researchers found a decrease in redness and swelling at the vaccination site when antipyretic/analgesic medication was administered prior to or at the time of vaccination, although these findings were not always statistically significant (Díez-Domingo et al., 1998; Hayat et al., 2011; Ipp et al., 1987; Lewis et al., 1988; Prymula et al., 2009; Rose et al., 2013). Rose et al. (2013) found the reduction of redness and swelling with prophylactic antipyretic/analgesic medication varied ( $P=0.017$  to  $P=0.475$ ) depending on the type of vaccine administered and number of the dose in the vaccine series. In four studies, there were 1% to 13% fewer reports of swelling in the treatment group



when compared to the control group (Díez -Domingo et al., 1998; Hayat et al., 2011; Lewis et al., 1988; Primula et al., 2009).

Findings were only statistically significant in one study where Ipp et al. (1987) noted a 9% reduction ( $P<0.025$ ) in cases of vaccine-related redness at the injection site in patients who received acetaminophen prior to or at the time of vaccination when compared with the placebo group. Ipp et al. (1987) also found decreased incidence of swelling and that patients receiving prophylactic acetaminophen were less likely to restrict movement of their legs; however, these findings were not statistically significant. Contrastingly, two studies published by Jackson et al. (2006) (N=387) and Yalcin et al.(2008) (N=270) found no consistent difference in redness or swelling between the group receiving the antipyretic/analgesic and the placebo group.

**Pain.** The effect of analgesic medication on vaccine-related pain at the injection site was evaluated in six studies (Díez-Domingo et al., 1998; Hayat et al., 2011; Ipp et al., 1987; Lewis et al., 1988; Prymula et al., 2009; Yalçin et al., 2008). There was a statistically significant decrease in vaccine-related pain in patients who received prophylactic treatment with an analgesic medication in two of the studies. In a series of three vaccine administrations, Díez-Domingo et al. (1998) found that mild pain was less frequent and less intense in the group receiving prophylactic antipyretic/analgesic compared to the control group after the first two vaccination doses ( $P<0.05$ ). Additionally, Ipp et al. (1987) found that parents reported vaccine-related pain less frequently in children who received an antipyretic/analgesic at the time of vaccination ( $P<0.001$ ). Four studies, with sample sizes ranging from N=270 to N=459 found no statistically significant decreases in vaccine-related pain at the injection site with prophylactic antipyretic/analgesic administration (Hayat et al., 2011; Lewis et al., 1988; Prymula et al., 2009; Yalçin et al., 2008).

## Systemic Vaccine Reactions

**Elevated temperature.** While 10 studies investigated the effect of antipyretic/analgesic medication on elevated temperature secondary to vaccination, (Dhingra & Mishra, 2011; Díez-Domingo et al., 1998; Hayat et al., 2011; Ipp et al., 1987; Jackson et al., 2011; Lewis et al., 1988; Prymula et al., 2009; Rose et al., 2013; Uhari et al., 1988; Yalçın et al., 2008) the timing of medication administration varied among the studies.

**Administration scheduled.** Eight studies investigated the effects of antipyretic/analgesic medication administration before, at the time of, or after vaccination. Four of the eight studies found a significant reduction in elevated temperature (Hayat et al., 2011; Ipp et al., 1987; Lewis et al., 1988; Rose et al., 2013). Hayat et al. (2011) studied the effect of prophylactic antipyretic/analgesic medication on infants aged 6-weeks, 10-weeks, and 14-weeks, as well as toddlers aged 18-months. When an antipyretic/analgesic medication was given one hour before vaccination and again 6, 12, and 18-hours after vaccination, the incidence of elevated temperature was significantly decreased in every age group ( $P<0.02$ ). Similarly, Lewis et al. (1988) reported that elevated temperatures were less frequent in patients who received an antipyretic/analgesic medication before vaccination and again at 3, 7, 12, and 18 hours following vaccination. While not statistically significant, participants who were 2-months old demonstrated the most marked difference with nearly a 60% reduction in elevated temperature ( $P=0.065$ ) (Lewis et al., 1988).

In another study, there was a statistically significant reduction in vaccine-related elevated temperatures ( $P<0.001$ ) when the antipyretic/analgesic medication was administered at the same time as the vaccination (Rose et al., 2013). When antipyretic/analgesic medication was

given immediately after vaccination, Ipp et al. (1988) found a significant reduction ( $P < 0.0005$ ) in elevated temperatures in infants ages 2-6 months.

Contrastingly, in four other studies (Díez-Domingo et al., 1998; Jackson et al., 2011; Uhari et al., 1988; Yalçın et al., 2008) researchers did not find a statistically significant difference with the incidence of elevated temperature between patients who received antipyretic/analgesic medication before or at the time of vaccination and patients who were not treated with antipyretic/analgesic medication.

***Administration as-needed.*** When parents could administer an antipyretic/analgesic medication on an as-needed basis, rather than prophylactically, there was a statistically significant higher incidence of elevated temperature ( $P=0.04$ ) during the first 6 hours following vaccination (Dhingra & Mishra, 2011).

***Administration in series.*** Prymula et al. (2009) measured elevated temperatures in infants after receiving the initial vaccination for DTaP, Hepatitis B, and IPV/Hib and again after receiving the second vaccination in each of the series. An elevated temperature  $>39.5^{\circ}\text{C}$  was uncommon ( $\leq 2\%$ ) in both the placebo and antipyretic/analgesic medication groups for both the initial and second vaccination. However, an elevated temperature  $>38^{\circ}\text{C}$  was 24% higher in the placebo group after the initial vaccine and 22% higher after the second vaccine in the series.

***Fussiness.*** The effect of prophylactic antipyretic/analgesic medication on behavioral changes post-vaccination, such as fussiness or irritability, was researched in eight studies (Dhingra & Mishra, 2011; Díez-Domingo et al., 1998; Hayat et al., 2011; Ipp et al., 1987; Jackson et al., 2011; Lewis et al., 1988; Prymula et al., 2009; Yalçın et al., 2008). Fewer incidents of post-vaccination fussiness were reported in four studies with the use of prophylactic antipyretic/analgesic medication (Hayat et al., 2011; Ipp et al., 1987; Jackson et al., 2011; Lewis

et al., 1988). In three of these studies, researchers reported the reduction in fussiness was statistically significant:  $P < 0.0001$  (Ipp et al., 1987),  $P = 0.01$  (Lewis et al., 1988), and  $P < 0.02$  (Hayat et al., 2011). Jackson et al. (2011) reported a 10% reduction in incidence of post-vaccination fussiness with concurrent administration of an antipyretic/analgesic medication. While the findings of Jackson et al. (2011) were not statistically significant, a 10% reduction in fussiness could be considered clinically significant.

Díez-Domingo et al. (1998) measured post-vaccination fussiness with the administration of an antipyretic/analgesic medication for three separate DTP vaccinations in a series. Interestingly, there was a statistically significant decrease in post-vaccination fussiness ( $P < 0.05$ ), but only for the first DTP vaccination in the series. The second and third DTP vaccinations in the series had no statistically significant difference in fussiness between the children who received an antipyretic/analgesic medication prior to vaccination and those who did not (Diez-Domingo et al., 1998).

In contrast, researchers reported no statistically significant change in fussiness between children who received prophylactic treatment with an antipyretic/analgesic and those who received no treatment. However, there were 4.7%-8.8% fewer episodes of fussiness in the groups who received prophylactic treatment with an antipyretic/analgesic medication prior to vaccination when compared to the non-treatment groups (Dhingra, & Mishra, 2011; Prymula et al., 2009; Yalçın et al., 2008). Nevertheless, the differences between groups were not statistically significant.

**Sleep.** Interference with routine sleep patterns post-vaccination was evaluated in only one study (Franck et al., 2011). Franck et al. (2011) reported that infants who received prophylactic treatment with an antipyretic/analgesic medication slept less following vaccination

when compared with infants who were not treated with an antipyretic/analgesic medication prophylactically. The researchers speculated that while higher temperature may be a primary cause for increased sleep post-vaccination, prophylactic treatment with antipyretic/analgesic decreased fever, thus decreasing sleep time. Interestingly, and statistically significant, was the timing of the vaccine administration. Infants receiving vaccinations after 1:30 p.m. had a longer sleep duration regardless of whether or not they received the antipyretic/analgesic medication with ( $P<0.007$ ) (Franck et al., 2011).

### **Antibody Response**

Researchers studied prophylactic treatment with antipyretic/analgesic medications prior to or at the time of vaccination and its effect on ability to mount an appropriate post-vaccination immune response (Prymula et al., 2009; Prymula et al., 2013; Uhari et al., 1988). Uhari et al. (1988) reported no statistically significant difference in IgG antibodies in 5-month-old infants who received a prophylactic dose of antipyretic/analgesic medication when evaluated 6 weeks after receiving the DTP vaccine. However, in a sentinel study Prymula et al. (2009) found statistically significant lower antibody geometric mean concentrations (GMCs) in patients who received an antipyretic/analgesic medication prior to vaccination. The vaccine antibody response remained suboptimal, even with the administration of the next vaccine in the series in children who received a dose of antipyretic/analgesic medication (Prymula et al., 2009). However, during a follow up study researchers found the effect of antipyretic/analgesic administration prior to or at the time of vaccination had a questionable effect on antibody response (Prymula et al., 2013). Consequently, Prymula et al. (2013) concluded that changes in antibody response following antipyretic/analgesic medication did not always occur.

## Discussion

Short-term vaccination side-effects can be concerning for both parents and providers (Paul & Whibley, 2010). Despite unpleasant, albeit non-life threatening, localized and systemic vaccine side-effects, the US Department of Health and Human Services (2015) maintains that vaccines are safe and effective, save lives, protect others through herd immunity, save time and money, and help protect future generations from potentially deadly vaccine-preventable diseases. Nevertheless, if parents are anxious regarding common side-effects of vaccinations, namely pain, they may be reluctant to have their children vaccinated according to the current recommended schedule (Luthy, Beckstrand, & Peterson, 2009). Therefore, it is important to educate parents about how to effectively treat common vaccine side-effects.

The potential for post-vaccination fever is common and worrisome to some parents, although some parents fear the potential for seizure secondary to fever rather than the fever itself (Martins & Abecasis, 2016). Unfortunately, the American Academy of Pediatrics (AAP) (2012) offers little guidance on this subject although the AAP recommends prophylactic treatment with an antipyretic/analgesic medication only for vaccination with DTaP when there is a personal or family history of febrile seizures. Because observing a febrile seizure can be disturbing, parents should be warned about the potential for febrile seizures with every vaccination and simultaneously reassured that febrile seizures are generally shorter than 1-2 minutes, do not cause any permanent harm, and are uncommon after vaccinations (Centers for Disease Control and Prevention, 2015). In addition, education should include the fact that administering an antipyretic/analgesic medication does not actually reduce the chance of the child having a febrile seizure (National Health Service Choices, 2014).

Currently, evidence is insufficient to suggest an altered immune response with administration of a prophylactic antipyretic/analgesic with vaccinations. The controversy of holding administration an antipyretic/analgesic medication because of the potential to interfere with immunity is based on one, isolated study. It should be noted, however, the single study suggesting an adverse effect on antibody response still produced therapeutic levels in the majority of the participants (Prymula et al., 2009). This finding suggests that the antibody response, while potentially decreased, would not necessarily be impaired enough to be harmful to patients. Furthermore, the clinical significance of this single study is unknown (Drutz, 2016), as well as the effect on immunity when a complete series of vaccinations is administered. Thus, further exploration of a relationship between an antipyretic/analgesic medication and decreased antibody response is needed.

### **Implications for Nurse Practitioners**

It is important for NPs to consider these data in order to properly and accurately educate patients and families about antipyretic/analgesic medication use before or at the time of vaccination. The evidence suggests that administering prophylactic antipyretic/analgesic medication can effectively reduce the potential for fever and other post-vaccine side-effects. This evidence is especially important information for anxious parents who may hesitate to vaccinate their children due to fear of the side-effects. Knowing their children might be able to avoid discomfort may ease parental anxiety and encourage them to adhere to the recommended vaccination schedule.

However, not all children develop vaccine-related side-effects. Thus, it may not be necessary to administer an antipyretic/analgesic agent prophylactically. Delaying administration of antipyretic/analgesic medication until the child exhibits vaccine-related side-effects would be

appropriate. After considering the most common side-effects and discovering that prophylactic antipyretic/analgesic medication has not yet been proven to decrease antibody immune response, the best practice would be for NPs to offer the option of prophylactic antipyretic/analgesic medication only when parents are especially anxious about potential vaccine side-effects. Non-anxious parents should be advised to employ a watch and wait strategy, administering an antipyretic/analgesic medication only after the child exhibits vaccine-related side-effects.

### **Conclusion**

Educating parents about the use of prophylactic antipyretic/analgesic medication at the time of vaccination is an essential role of the NP. More research is needed on the effect of antipyretic/analgesic medications on local and systemic post-vaccination side-effects and on antibody response. However, with the available evidence, the best practice is to recommend parents administer an antipyretic/analgesic medication prophylactically if concerned about vaccine side-effects, or after the side-effects have manifested. Parents can be reassured that there is not yet enough evidence to avoid an antipyretic/analgesic based on its interference with antibody response. Nevertheless, NPs should remain up-to-date with the literature so they can wisely counsel patients and families regarding vaccination-related side-effects and the administration of antipyretic/analgesic medication.



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