REVIEW ARTICLE

Common Selfcare Indications of Pain Medications in Children

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Abstract

Pain has a multifaceted impact on individuals worldwide, affecting their physical functioning, emotional well-being, and quality of life. Children (age < 18 years) have a high prevalence of conditions associated with pain, such as toothache, headache, earache, sore throat, and respiratory tract infections, many of which may be accompanied by fever. Globally, the pharmacologic treatment of pain in pediatric patients is limited largely to nonopioid analgesics, and dosing must account for differences in age, weight, metabolism, and risk of adverse effects. This narrative review summarizes the findings of a literature search on the pediatric indications, dosing approaches, dosing guidelines, and pharmacokinetics of paracetamol and ibuprofen, which are common pain medications available globally for self-care use in children. The review also discusses the risks and benefits associated with these agents. The current roles of paracetamol and ibuprofen in the symptomatic management of coronavirus disease 2019 (COVID-19) infection and in the management of post–COVID-19 immunization symptoms in children are also discussed. Therefore, while a very large amount of data over several decades is available for paracetamol and ibuprofen, an urgent need exists for well-designed studies of these medications for the management of pain and fever in pediatric patients with COVID-19 to ensure optimal relief with minimal toxicity.

1 Introduction

Over 90% of individuals worldwide suffer from pain each year. The global burden of pain was demonstrated in a combined analysis of three international online surveys (editions 1, 2, and 3 of the Global Pain Index [GPI] study) carried out to quantify the perceived immediate impact of pain on individuals' lives [1]. Responses of ~ 29,000 individuals from 14 countries who were ≥ 18 years of age and had ever experienced musculoskeletal pain were analyzed [1]. Results indicated that for roughly half of the survey population, the burden of pain involves pain frequency of at least once weekly, pain duration of at least several hours, decreased ability to be happy, reduced quality of life, and impaired ability to enjoy life.

Pain is common among infants, children, and adolescents. Types of pain frequently experienced in pediatric populations are listed in Table 1 [2]. The fourth edition of the GPI study (GPI-4), which was carried out in 19 countries in 2020 to explore self-care of pain (includes parent-to-child treatment), included information on self-care of pain indications in children up to 18 years of age based on responses given by their parents. Results demonstrated that pain conditions

with a prevalence of > 50% in children ages ≤ 18 years (as reported by 7917 parents) are toothache (53%), earache (54%), headache (54%), fever and pain associated with vaccination/immunization (59%), stomachache (64%), respiratory tract infections (71%), and sore throat (72%) (GPI-4 unpublished data). Findings also demonstrated the burden of managing a child's pain on parents, with 73% reporting that their children are miserable or not their usual selves when they are in pain and prompting 40% to report feeling panicked and helpless [3].

Common pain medications available globally for use in children are paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drugs (NSAIDs); in many low- and middle-income countries, limited access to medications leaves these as the only medications available. Because of safety, addiction, and diversion concerns, opioids are not typically used to treat mild to moderate pain in the pediatric population. Metamizole (dipyrone), a cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2) inhibitor, is used in some countries for the treatment of pediatric pain conditions, despite the high risk for serious adverse effects, particularly agranulocytosis [4, 5]. Because of this risk, use of metamizole is banned in the United States and most Western European countries. A review of the literature concluded that no evidence existed to support the superiority of metamizole

over paracetamol or ibuprofen for pediatric analgesia and that such use should not be recommended or encouraged [4].

Paracetamol acts to relieve pain and fever. Its analgesic effect is not completely understood but is believed to be a direct action of the metabolite *N*-acylphenolamine on the brain and dorsal horn of the spinal cord [6]. Its antipyretic effect is thought to involve central nervous system inhibition of a COX-1 protein variant and potential inhibition of COX-2, as well as peripheral nervous system inhibition of transient receptor potential subfamily ankyrin 1 channels on sensory neurons by the liver metabolites *N*-acetyl-*p*-benzoquinoneimine and *p*-benzoquinone [7]. The central and peripheral nervous systems are also targets for the analgesic effects of paracetamol [7].

NSAIDs (e.g., ibuprofen) act to relieve pain, fever, and inflammation in children over 3 months of age [8]. Their effects result from inhibition of prostaglandin production from arachidonic acid via inhibition of COX-1 and COX-2 [9]. COX-1 and COX-2 are also called prostaglandin synthase and they have binding sites for COX and peroxidase. COX-1 is responsible for regulating normal cell processes and is expressed in most tissues. In contrast, COX-2 is constitutively active in the brain, kidney, and bone but is

normally not measurable in most other tissues [9]. Although both COX-1 and COX-2 lead to the production of prostaglandins, it is induction of COX-2 that leads to production of prostaglandins associated with inflammation. Nonselective NSAIDs inhibit both COX-1 and COX-2, while selective NSAIDs, also called COX-2 inhibitors, preferentially inhibit COX-2. However, data on the effects of COX-1/2 inhibition on inflammation are inconclusive [9].

The objectives of this narrative review are to summarize the findings of a literature search on common pediatric indications, dosing approaches, dosing guidelines, and pharmacokinetics of paracetamol and ibuprofen, common pain medications available for self-care use in children, and to discuss the associated risks and benefits. Their current roles in the symptomatic management of coronavirus disease 2019 (COVID-19) infection and in the management of post–COVID-19 immunization symptoms in children are also discussed.

2 Literature Analysis

The search identified 72 relevant studies and reviews and 20 sets of guidelines. Additional articles (ten studies, three reviews) and guidelines (13 articles) were included at the discretion of the authors. Among the studies and reviews, 31 included common indications of paracetamol and 25 included common indications of ibuprofen. A summary of the key clinical studies and meta-analyses of paracetamol and ibuprofen use in pediatric patients is presented in Table 2.

A literature search was conducted to retrieve published articles and guidelines on the common indications and dosing approaches of paracetamol and ibuprofen in pediatric patients. Additional articles and guidelines were included at the discretion of the authors.

The ProQuest (Derwent Drug File, Embase, MEDLINE, ToxFile) database was searched for English-language articles published through September 2022 (strategy outlined in Supplementary Table 1, see the electronic supplementary material). Inclusion criteria were the following: clinical studies, systematic reviews, and review articles (meta-analyses)

Table 1 Types of pain frequently experienced in pediatric populations [2, 102]

Symptom	Estimated incidence	Population	Risk factors
Headache	54.4%	Children and adolescents	Female sex and age
Abdominal pain	49.8%	Adolescents	Female sex
Musculoskeletal pain	30%	Children 10–12 years of age	Female sex and age
Growing pains	2.6–49.4%	Children	Age
Dental pain	25% in children 5 years of age 48–88% in children 8–10 years of age	Children 5–10 years of age	Dental caries

Table 2 Key clinical studies and meta-analyses of paracetamol and ibuprofen use in pediatric patients [28–30, 32, 33, 36–40, 45–47, 49–55, 62–75, 77, 80, 84, 103–108]

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Fever						
Okereke et al. (2021) [29]	To compare the efficacy of paracetamol syrup and dispersible tablets for the treatment of fever	Randomized, controlled, double-blind, single-dose study	N = 74 (6 months–12 years)	Paracetamol syrup 15 mg/kg vs. dispersible tablets 15 mg/kg	Reduction in tympanic temperature from baseline to 1 h post dosing	Both preparations exhibited statistically comparable antipyretic effects
Magni et al. (2011) [71]	To compare the efficacy of ibuprofen and dipyrone for childhood fever	Randomized, open-label, single-dose study	N = 80 (6 months–8 years)	Ibuprofen 10 mg/kg vs. dipyrone 15 mg/kg	Reduction in temperature from baseline at 2, 3, 4, 5, 6, 7, and 8 h after dosing	Ibuprofen had greater antipyretic efficacy than dipyrone
Alaje et al. (2020) [30]	To assess the effectiveness and safety of a single dose of ibuprofen vs. paracetamol for treating childhood fever	Randomized, controlled, single-dose study	N = 140 (6–59 months)	Paracetamol 15 mg/kg vs. ibuprofen 10 mg/kg	Reduction in tympanic temperature from baseline to 6 h post dosing	Paracetamol was less effective than ibuprofen
Tan et al. (2020) [28]	To compare the antipyretic, analgesic, and safety profile of paracetamol with ibuprofen	Systematic review and meta-analysis	N = 241,138 children (< 2 years) from 19 studies	Paracetamol (≤ 10 vs. > 10 mg/kg) and ibuprofen (≤ 5 vs. > 5 mg/kg)	Fever (continuous variable) or pain within 4 h of treatment onset	Paracetamol had lower efficacy on reducing fever and pain vs. ibuprofen
Paul et al. (2010) [49]	To compare the antipyretic effect of a single dose of ibuprofen, ibuprofen plus paracetamol, and ibuprofen followed 3 h later by paracetamol (alternating regimen)	Randomized, controlled study	N = 60 (6 months–8 years)	Ibuprofen 10 mg/kg vs. ibuprofen 10 mg/kg plus paracetamol 15 mg/kg vs. ibuprofen 10 mg/kg followed by paracetamol 15 mg/kg (alternating regimen)	Temperature difference between treatment groups	Ibuprofen plus paracetamol had significantly greater antipyretic effect at hour 4 ($P = 0.002$), 5 ($P<0.001$), and 6 ($P < 0.001$). Alternating regimen also had a significantly greater antipyretic effect than ibuprofen alone at hour 4 ($P = 0.003$), 5 ($P < 0.001$), and 6 ($P < 0.001$)
Thomas et al. (2008) [62]	To compare the antipyretic effect of tepid sponging and paracetamol vs. paracetamol alone	Randomized, controlled study	N = 150 (6 months–12 years)	Paracetamol 10 mg/kg with sponging for 15 minutes vs. paracetamol 10 mg/kg	Reduction in body temperature and level of comfort	Reduction in body temperature was faster with tepid sponging plus paracetamol than paracetamol, while the level of discomfort was significantly higher with tepid sponging plus paracetamol than paracetamol alone ($P < 0.001$)

Table 2 (continued)

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Kramer et al. (2008) [50]	To compare the antipyretic effect of paracetamol alternated with placebo vs. paracetamol alternated with ibuprofen	Randomized, prospective, double-blind, placebo-controlled study	$N = 38$ (6 months–6 years)	Paracetamol 15 mg/kg alternated with placebo vs. paracetamol 15 mg/kg alternated with ibuprofen 10 mg/kg	Reduction in fever	Alternating regimen of paracetamol and ibuprofen showed significantly higher reduction in fever at hour 4 ($P = 0.05$) and 5 ($P = 0.003$)
Hay et al. (2008) [51]	To compare the antipyretic effect of multiple doses of paracetamol plus ibuprofen compared with either drug alone	Randomized, blinded, controlled study	$N = 156$ (6 months–6 years)	Paracetamol 15 mg/kg and ibuprofen 10 mg/kg	Number of minutes without fever (< 37.2 °C) in the first 4 h and proportion of children reported as being normal on the discomfort scale at 48 h	Paracetamol plus ibuprofen was significantly superior to paracetamol alone in the first 4 h ($P < 0.001$) but not to ibuprofen alone ($P = 0.2$)
Wong et al. (2001) [63]	To compare the antipyretic effect of paracetamol, dipyrone, and ibuprofen	Randomized, multiracial, multinational (Brazil, Argentina/Chile, and Mexico), multicenter, prospective, modified double-blind, parallel-group study	$N = 628$ (6 months–6 years)	Dipyrone 15 mg/kg vs. paracetamol 12 mg/kg (average) vs. ibuprofen (5 mg/kg for temperature < 39.2 °C and 10 mg/kg for temperature ≥ 39.2 °C)	Reduction in fever	All 3 medications were effective in reducing temperature. Temperature normalization rates with ibuprofen and dipyrone were significantly higher than with paracetamol ($P = 0.004$)
Lesko and Mitchell (1999) [64]	To assess the safety of paracetamol and ibuprofen	Practitioner-based, double-blind, clinical study	$N = 27{,}065$ (< 2 years of age)	Paracetamol (12 mg/kg) or ibuprofen in 1 of 2 doses (5 or 10 mg/kg)	Rates of hospitalization for specific diagnoses according to antipyretic assignment	Rate of serious adverse clinical events requiring hospitalization among febrile children treated with paracetamol and ibuprofen were low, with no significant difference between the 2 medications
Kinmonth et al. (1992) [74]	To compare the acceptability and antipyretic effect of the addition of paracetamol or warm sponging to simple unwrapping	Randomized, open, parallel-group study	$N = 52$ (3 months–5 years)	Paracetamol (120 mg ≤ 1 year and 240 mg > 1 year)	Reduction in fever and acceptability of treatment	Paracetamol was more effective in controlling fever and was acceptable to children and parents as a home treatment
Friedman and Barton (1990) [52]	To compare the antipyretic effect of sponging, sponging plus paracetamol, and paracetamol alone	Randomized study	$N = 73$ (4 months–4 years)	Paracetamol 10–15 mg/kg	Reduction in temperature	The greatest reduction in temperature was recorded with sponging plus paracetamol and the smallest reduction with sponging alone

Table 2 (continued)

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Kramer et al. (1991) [75]	To assess risks and benefits of paracetamol in young children with acute fever of presumed viral origin	Randomized, double-blind, placebo-controlled study	N = 225 (6 months–6 years)	Paracetamol 10–15 mg/kg every 4 h vs. placebo	Duration of fever and improvements in 6 specific aspects of comfort and behavior	Paracetamol did not prolong the duration of fever and led to improvement in activity and alertness in ~ 1/3 of treated children
Vauzelle-Kervroedan et al. (1997) [65]	To demonstrate equivalence between paracetamol and ibuprofen	Randomized, double-blind, multicenter equivalence study	N = 120 (4.1 ± 2.6 years [range 0.67–11.92 years])	Ibuprofen 10 mg/kg vs. paracetamol 10 mg/kg	Main criterion for equivalence was the time elapsed between drug administration and the lowest temperature observed between hours 0–6	Ibuprofen and paracetamol, administered as Sparklets showed equivalence with respect to the time elapsed between dosing and the lowest observed temperature within 6 h
Walson (1990) [53]	To compare the efficacy and toxicity of ibuprofen liquid with paracetamol elixir	Double-blind single- and multiple-dose studies	Single dose: N = 127 (2–11 years) Multiple dose: N = 64 (2–11 years)	Single dose: Ibuprofen 5 and 10 mg/kg vs. paracetamol 10 mg/kg Multiple dose: Ibuprofen 2.5, 5, and 10 mg/kg vs. paracetamol 10–15 mg/kg	Antipyretic efficacy	Single dose: Ibuprofen 10.0 > paracetamol 10.0 = ibuprofen 5.0 > placebo Multiple dose: Ibuprofen 10.0 = paracetamol 15.0 > ibuprofen 5.0 > ibuprofen 2.5 mg/kg
Sidler et al. (1990) [66]	To compare the antipyretic efficacy and safety of ibuprofen and paracetamol	Double-blind, parallel-group, multicenter study	N = 89 (5 months–13 years)	Ibuprofen syrup at 7 mg/kg and 10 mg/kg vs. paracetamol 10 mg/kg	Reduction in temperature and incidence and severity of side effects	Reduction in temperature was significantly lower with ibuprofen 7 mg/kg ($P \leq 0.05$) and 10 mg/kg ($P \leq 0.01$) compared with paracetamol. Both medications were well tolerated
Thompson et al. (1987) [67]	To compare the therapeutic efficacy and adverse effects of paracetamol and rimantadine in the treatment of acute influenza A infection	Randomized, double-blind study	N = 63 (1–12 years)	Paracetamol (10 mg/kg/day given orally every 6 h up to a maximum of 360 mg/day) plus placebo vs. rimantadine (6.6 mg/kg/day given orally every 12 h up to a maximum of 200 mg/day) plus placebo	Illness scores calculated by assigning points to the most common symptoms of influenza	There were no significant differences between rimantadine and acetaminophen in their effectiveness in controlling the symptoms or overall course of the disease; both medications were well tolerated without any discernible side effects

Table 2 (continued)

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Southey et al. (2009) [103]	To compare the tolerability and safety between ibuprofen and paracetamol when used as antipyretic and analgesic agents	Systematic review and meta-analysis	Children (0–18 years)	Paracetamol vs. ibuprofen vs. placebo	Tolerability and safety, which included serious adverse events that were fatal, life threatening, or required hospitalization; serious adverse events that did not require hospitalization; adverse events that required discontinuation of medication; systemic reactions related to the use of ibuprofen or paracetamol	Comparable tolerability and safety profiles were noted for ibuprofen, paracetamol, and placebo, particularly in terms of gastrointestinal symptoms, asthma, and renal adverse effects
Yin et al. (2022) [104]	To compile published research comparing ibuprofen and acetaminophen in the treatment of infectious fever	Meta-analysis	Children with infectious fever (2–8 years)	Ibuprofen vs. paracetamol	Reduction in temperature and adverse events	A significant reduction in fever was noted with ibuprofen vs. paracetamol at 4 h ($P < 0.00001$); no significant differences were noted in adverse events for the 2 medications
Abdominal pain						
Poonai et al. (2020) [32]	To compare the efficacy of paracetamol to hyoscine butylbromide in children with nonspecific colicky abdominal pain	Randomized, controlled, double-blind clinical study	N = 236 children and adolescents (8–17 years)	Paracetamol (15 mg/kg, maximum 975 mg) vs. hyoscine butylbromide (10 mg)	Minimal clinically important difference for self-reported pain at 80 min of 13 mm on a 100 mm visual analog scale	Paracetamol and hyoscine butylbromide had comparable efficacy

Table 2 (continued)

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Dental pain						
Raslan and Zouzou (2021) [33]	To compare the efficacy of preemptive paracetamol or ibuprofen with placebo in reducing pain during injection, extraction, and postoperatively	Randomized, placebo-controlled, triple-blinded clinical study	N = 60 children (6–8 years) undergoing primary tooth extraction	Paracetamol 320 mg vs. ibuprofen 200 mg vs. placebo	Pain level after injection, extraction, and postoperatively	Pretreatment with paracetamol and ibuprofen exhibited significant differences in pain scores vs. placebo, and ibuprofen pretreatment resulted in significantly lower pain scores vs. paracetamol immediately after injection, immediately after extraction, and at 3, 4, and 5 h after extraction ($P < 0.05$)
Baillargeau et al. (2020) [38]	To evaluate discomfort after extraction of deciduous teeth under local anesthesia and to describe paracetamol usage	Prospective observational study	N = 125 children (3–13 years)	Paracetamol 15 mg/kg	Pain level	One dose of paracetamol was adequate in the majority of the children; only 7 received a second dose, and no third dose was required
Fux-Noy et al. (2020) [39]	To compare the efficacy of preoperative paracetamol in reducing postoperative pain after routine dental treatment	Randomized, placebo-controlled, parallel-group clinical study	N = 102 children (5–12 years)	Paracetamol 15 mg/kg vs. placebo	Post-operative pain level	Preoperative paracetamol had no effect on pain in pediatric patients receiving routine dental treatment
Bird et al. (2007) [105]	To compare pain control effectiveness of paracetamol and ibuprofen taken 1 h before separator placement	Prospective, randomized, double-blind clinical study	N = 40 (9–19 years)	Paracetamol 650 mg vs. ibuprofen 400 mg	Reduction in pain	Time had a significant influence on pain ($P = 0.0001$), with pain increasing immediately after separator placement, lessening, and then increasing to a peak, the following morning. No difference was noted in pain levels between paracetamol and ibuprofen
O'Donnell et al. (2007) [68]	To investigate difference in the pain levels following dental extractions of primary teeth with preoperative paracetamol, intraoperative Voltarol, or no analgesia	Tri-sited study	N = 210 (3–12 years)	Paracetamol 20 mg/kg 30 min before the procedure vs. rectal Voltarol 25 mg 1–2 min prior to the extraction	Post-operative pain level	Reduction in pain was significant with preoperative paracetamol ($P < 0.01$) and Voltarol ($P < 0.001$) compared with no analgesia

Table 2 (continued)

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Primosch et al. (1995) [106]	To evaluate efficacy of preoperative administration of ibuprofen and paracetamol vs. placebo for pain relief after primary teeth extractions	Randomized blinded study	N = 60 (2–10 years)	Paracetamol 240–480 mg vs. ibuprofen 150–300 mg (depending on age)	Reduction in pain	No statistically significant difference was noted in pain reduction with preoperative administration of paracetamol and ibuprofen; however, over half the parents perceived that the reported pain was sufficient to warrant postoperative analgesic administration
Headache and migraine						
Pavithra et al. (2020) [40]	To compare paracetamol and ibuprofen for the management of acute headache in children with migraine without aura	Randomized, controlled, parallel-group, double-blind clinical study	N = 50 (6–12 years)	Paracetamol 15 mg/kg/dose vs. ibuprofen 10 mg/kg/dose	Pain freedom and pain relief 2 h after drug intake	Paracetamol was comparable to ibuprofen for pain freedom (32% vs. 28%; P = 0.77) and pain relief (80% vs. 80%; P = 0.86)
Wang et al. (2020) [77]	To assess the efficacy of medications used in pediatric migraine treatment	Network meta-analysis	Children and adolescents (< 18 years) with migraine	–	–	NSAIDs (including paracetamol, ibuprofen, and ibuprofen suspension) were effective for pain relief
Cuvellier et al. (2009) [107]	To collect data on headache treatment in neuro-pediatric departments	Prospective, multicenter study	N = 479 (2–16 years)	–	–	Paracetamol (83%) and NSAIDs (54%) were the most frequently prescribed acute treatments, while ergot alkaloids (7%) were the most frequently prescribed prophylactic treatment for headache
Dooley et al. (2007) [73]	To assess the role of caffeine with ibuprofen in the treatment of pediatric headache	Randomized double-blind, placebo-controlled pilot study	N = 12 (< 16 years)	Ibuprofen 100–400 mg (depending on body weight) plus caffeine (50–100 mg) vs. ibuprofen plus placebo	Five-faces severity scale, measure of clinical disability, and scale of pain severity	7/12 children obtained faster relief with ibuprofen plus caffeine. Cumulative response scores for the 3 outcome measures showed a trend toward a greater response to the combination treatment

Table 2 (continued)

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Silver et al. (2008) [108]	To compile a single data set of all randomized clinical trials evaluating the acute treatment of pediatric migraine	Meta-analysis	Pediatric patients with headache/migraine	Paracetamol, ibuprofen, zolmitriptan, sumatriptan, rizatriptan, dihydroergotamine	Headache/pain relief	Only ibuprofen and sumatriptan have shown statistically significant pain and headache relief in pediatric patients compared with placebo
Sore throat						
Ruperto et al. (2011) [37]	To confirm the analgesic effect and tolerability of paracetamol and to compare the efficacy of paracetamol, ketoprofen lysine salt, and placebo	Randomized, double-blind, single-dose, parallel group, placebo-controlled study	$N = 97$ children	Paracetamol 12 mg/kg vs. ketoprofen lysine salt 40 mg vs. placebo	Sum of Pain Intensity Differences score rated by the child	Paracetamol was significantly more effective than placebo on the Sum of Pain Intensity Differences scores of children and parents ($P = 0.0171$) and was well tolerated
Musculoskeletal injuries						
Poonai et al. (2014) [72]	To compare the efficacy of ibuprofen and morphine for the relief of fracture-related pain	Randomized, blinded, parallel-group superiority study	$N = 134$ children	Ibuprofen 10 mg/kg vs. morphine 0.5 mg/kg	Change in pain score on the Faces Pain Scale–Revised before and after the first dose	Both drugs had similar efficacy, but ibuprofen was more tolerable
Tonsillectomy/adenotonsillectomy						
Mahgoobifard et al. (2014) [45]	To compare the analgesic effects of preoperative administration of paracetamol and ibuprofen	Randomized, double-blind, placebo-controlled study	$N = 60$ children	Paracetamol 15 mg/kg vs. ibuprofen 10 mg/kg vs. placebo	Mean post-surgical pain scores	Patients who received paracetamol 30 min before surgery experienced significantly less pain than those who received ibuprofen or placebo ($P < 0.05$)
Mirashrafi et al. (2021) [46]	To compare the effects of pre- and postoperative administration of paracetamol and ibuprofen on pain, bleeding, nausea, and vomiting after surgery	Randomized, double-blind study	$N = 50$ children	Paracetamol 15 mg/kg vs. ibuprofen 10 mg/kg	Wong-Baker Visual Analog Scale Episodes of postoperative bleeding, nausea and vomiting	No difference in pain scores or bleeding; ibuprofen was associated with fewer vomiting episodes on the first postoperative day
Jotić et al. (2019) [47]	To compare the analgesic effects of paracetamol and ibuprofen for postoperative pain management	Randomized clinical study	$N = 147$ children	Paracetamol 10–15 mg/kg vs. ibuprofen 10 mg/kg every 6 h	Visual analog scale	No significant differences were found between treatment groups

Table 2 (continued)

Post-vaccination symptoms

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Jackson et al. (2006) [54]	To determine if prophylaxis with paracetamol or ibuprofen can reduce risk of local reactions after the fifth DTaP vaccination	Randomized, blinded, controlled study	$N = 387$ (4–6 years)	Paracetamol 15 mg/kg up to a maximal dose of 450 mg or ibuprofen 10 mg/kg, up to a maximal dose of 300 mg vs. placebo	Reduction in risk of local reactions	No significant reduction in risk of local reactions with paracetamol or ibuprofen compared with placebo
Uhari et al. (1988) [69]	To evaluate the prophylactic effectiveness of paracetamol in preventing or lessening of DTP vaccination-associated fever and other reactions in healthy infants	Randomized, double-blind study	$N = 263$ (5 months)	Paracetamol 75 mg vs. placebo	Prophylaxis of vaccine-induced fever	Mean temperature was the same with a single dose of paracetamol and placebo in the evening and next morning
Ipp et al. (1987) [55]	To evaluate the prophylactic effectiveness of paracetamol in preventing adverse reactions to DTP-polio vaccine	Randomized, placebo-controlled, double-blind study	$N = 382$ (2–6 months); $N = 70$ (18 months)	Paracetamol 15 mg/kg/dose every 4 h	Local and systemic reactions and incidence of fever	Paracetamol significantly reduced local ($P < 0.025$) and systemic reactions ($P < 0.05$) and incidence of fever ($P < 0.0005$) among infants 2–6 months of age. The differences were not statistically significant with paracetamol compared with placebo after the booster at 18 months
Lewis et al. (1988) [84]	To evaluate the prophylactic effectiveness of paracetamol in preventing reactions to DTP vaccine	Double-blind controlled study	$N = 282$ (2 months–6 years)	Paracetamol 40–240 mg (depending on age) vs. placebo	Reaction scores post-vaccination based on the presence of each of 10 variables (temperature ≥ 38.0 °C, local redness, local swelling, local induration, local pain, sleepiness, anorexia, fussiness, vomiting, and crying for ≥ 30 min)	The overall reaction rates were lower with paracetamol than placebo, with beneficial effects particularly noted in reducing fever, pain, and fussiness

Table 2 (continued)

Reference	Objective	Study design	Study population	Treatment	Primary outcome	Key finding
Prymula et al. (2009) [70]	To assess the effect of prophylactic administration of paracetamol at vaccination on infant febrile reaction rates and vaccine responses (PHiD-CV + DTPa/HBV/IPV/Hib + HRV, followed by a booster dose of PHiD-CV plus DTPa/HBV/IPV/Hib)	Two consecutive (primary and booster) randomized, controlled, open-label vaccination studies	N = 459 (9–16 weeks at time of enrollment); N = 415 (12–15 months at time of boosting)	Paracetamol (80–125 mg, depending on weight) vs. no prophylactic paracetamol	Febrile reactions	The percentage of children with temperature of ≥ 38 °C after at least 1 dose was significantly lower (no overlap of 95% CIs) in the prophylactic paracetamol group after primary vaccination and booster vaccination than in the no-prophylactic paracetamol group

CI confidence interval, *DTaP* diphtheria-tetanus-acellular pertussis vaccine, *DTP* diphtheria-tetanus-pertussis vaccine, *HBV* hepatitis B vaccine, *Hib Haemophilus* influenzae type B vaccine, *IPV* inactivated polio vaccine, *NSAID* nonsteroidal anti-inflammatory drug, *HRV* human rotavirus vaccine, *PHiD-CV Hemophilus influenzae* protein D-conjugate vaccine

on the effectiveness and safety of paracetamol, ibuprofen, and NSAIDs in children; studies in common indications (e.g., fever, pain, migraine/headache, muscle ache, sore throat, musculoskeletal pain, fever and pain associated with vaccination/immunization, pain after dental procedures/tooth extraction, toothache, earache/otalgia, respiratory tract infections including cold and flu, COVID-19); and studies including medications with oral routes of administration (tablets/capsules/suspensions). Articles were excluded if they described studies in prescription indications, such as febrile seizures, lower abdominal surgeries, perineal surgeries, spinal surgeries, concussion (mild traumatic brain injury), and patent ductus arteriosus, if the studies did not use standard doses of paracetamol (10–15 mg/kg; 60 mg/kg/day) or ibuprofen (5–10 mg/kg; 30 mg/kg/day), if they were in a language other than English, or if they were conducted in adolescents and adults. Nonclinical studies, case reports, letters, comments, and editorials were also excluded.

To fully capture relevant safety-related pharmacokinetic data on paracetamol use in the pediatric population, we conducted additional searches on the clinical pharmacology of paracetamol pediatric formulations from the last 3 years (30 June 2019–30 September 2022; Supplemental Table 2).

Country-specific guidelines on the use of paracetamol and ibuprofen in the management of pediatric indications were reviewed to identify areas of consensus. Health authority guidelines (e.g., those from the Centers for Disease Control and Prevention [CDC], National Institutes of Health [NIH], and World Health Organization [WHO]) on the symptomatic management of COVID-19 infection in children and on the management of post-vaccine symptoms in children eligible to receive COVID-19 vaccines, as well as current prescribing information for the available COVID-19 vaccines (Pfizer-BioNTech [COMIRNATY], Moderna, Johnson & Johnson/Janssen, and Sinovac [CoronaVac] vaccines) were reviewed to provide information on the roles of paracetamol and ibuprofen in these applications.

3 Pharmacokinetics

3.1 Paracetamol

Paracetamol is a highly lipid-soluble compound with a maximum observed concentration (C_{max}) of 12.6 µg/mL, a time to reach C_{max} (t_{max}) of ~ 2 h, and an elimination half-life ($t_{1/2}$) of ~ 2.3 h in children for the 15 mg/kg dose of its oral formulation [10]. Variations have been noted across formulations; for example, a $t_{1/2}$ of 3.8 h has been recorded using paracetamol suppositories in neonates [11]. Oral paracetamol is rapidly absorbed with a mean systemic availability of ~ 75% [12]. Paracetamol is primarily eliminated by glucuronidation and sulfation pathways, which have been reported to

be 55% and 30% of the total urinary excretion, respectively [12, 13]. However, some aspects of the pharmacokinetics of paracetamol vary by age owing to maturation processes and developmental growth [14–17]. For example, absorption is slower (longer time to C_{max}) and clearance increases exponentially over the first 12 months of life (4.9 L/h/70 kg at birth to 12.4 L/h/70 kg by 12 months) [15]. The clearance in infants is reported to be 80% that of a 2-year-old child by 6 months of age [15]. In a population pharmacokinetic analysis of paracetamol in premature neonates and infants, the volume of distribution decreased exponentially from 109.7 L/70 kg at 28 weeks to 72.9 L/70 kg by 60 weeks after conception, with a maturation half-life of 11.5 weeks [16]. Clearance increased from 0.74 L/h/70 kg at 28 weeks to 10.8 L/h/70 kg at 60 weeks, with a maturation half-life of 11.3 weeks [16]. In addition, $t_{1/2}$ is longer for neonates than for older children. The $t_{1/2}$ of paracetamol is 2.5–4 h in neonates, 11 h for 28- to 32-week-old neonates (for rectally administered paracetamol), and 4–5 h in 32- to 36-week-old neonates [14]. A relationship between glucuronide clearance and age has been suggested in neonates and children, wherein glucuronide clearance has been shown to increase with age [14]. This is expected, as the sulfation pathways mature at birth, while the glucuronidation pathways mature around 2 years of age [14]. In addition to the two phase II metabolic pathways, a small proportion (~ 2%) of unchanged paracetamol is eliminated in the urine [18]. The remainder (~ 10%) undergoes phase I oxidation by hepatic cytochrome P450 2E1 (CYP2E1) (and to a lesser extent with CYP1A2 and CYP3A4), which leads to the formation of a highly reactive toxic metabolite, *N*-acetyl-para-benzo-quinone imine (NAPQI) [18]. Evidence suggests that the hepatotoxicity associated with paracetamol overdose may occur through the formation of the toxic NAPQI metabolite, which has been detected in excessive levels in those exposed to very high doses of paracetamol [18]. The excessive formation of NAPQI leads to glutathione depletion, oxidative stress, and mitochondrial dysfunction, ultimately resulting in the cessation of adenosine triphosphate (ATP) synthesis [18]. However, large-scale studies are required to correlate these findings and to understand the link between the toxic and analgesic effects of paracetamol with specific genotypes in order to improve the benefit–risk ratio of paracetamol with adapted pharmacogenetic screening [19].

In addition to age, body weight is another factor accounting for variation in the pharmacokinetics of drugs that undergo hepatic metabolism, such as paracetamol [20, 21]. When comparing standard weight-based dosing regimens of paracetamol, clearance increases from birth through childhood. Two studies showed that the dosing for obese or overweight children required significantly higher paracetamol dosages; however, the dosages received were either lower or even higher than the recommended dosage (10–15 mg/day),

without necessary dose alteration, compared with children of healthy weight [22, 23]. A multicenter prospective observational cohort study in the United Kingdom found that the median (interquartile range) dose of oral paracetamol (mg/kg) was significantly lower ($P < 0.001$) for obese versus non-obese children 2–16 years of age, despite obese children requiring significantly greater analgesia more frequently in the post-anesthetic care unit than children of healthy weight ($P = 0.04$) [22]. In contrast, another prospective UK study showed that obese or overweight children received paracetamol at greater than formulary dosing standards compared with healthy children, without adequate adjustment according to ideal body weight or lean body mass, which may result in drug toxicity [23]. As concluded from recently published literature analysis findings, data supporting recommendations for paracetamol dosing strategies for pain and fever in obese and overweight children are limited, placing such children at increased risk for adverse outcomes or suboptimal efficacy [24]. Overall, the available information on the pharmacokinetics of paracetamol in children suggests that weight-based dosing should provide acceptable efficacy and safety.

3.2 Ibuprofen

Ibuprofen is rapidly absorbed from the stomach, with a C_{max} of 35.8 mg/L, t_{max} of 0.74 h, and $t_{1/2}$ of 6 h in children. Its antipyretic effect generally lasts approximately 6 h [25], and time to onset of the antipyretic effect is shortest for the liquid formulation compared with tablets [26]. The influence of age and weight on the pharmacokinetics of ibuprofen has not been thoroughly studied; however, the results of maturation modeling investigations demonstrated that the clearance of ibuprofen in term infants was 90% of adult levels by 1 month of age and 98% of adult levels by 3 months of age, with a maturation half-life of 36.8 weeks [27].

In younger infants at risk for dehydration, the use of ibuprofen has been associated with acute kidney injury [26, 28]. Overdose in children is rare [26]. Consequently, the limited information on the pharmacokinetics of ibuprofen in children suggests that it is effective and safe in most clinical situations, with specific exceptions identified.

4 Dosing Approaches

4.1 Paracetamol

Multiple formulations of paracetamol are available for use in children (e.g., liquids, solutions, syrups, suspensions, tablets, suppositories, and intravenous formulations) [29–37]. However, as this review describes the use of paracetamol for self-care, intravenous formulations have not been

discussed. Formulations are typically selected according to each patient's specific situation to provide the optimum delivery of medication. Most studies [23, 29, 30, 32, 36, 38–55] and guidelines [26, 56–59] support administration of oral paracetamol at a dose of 15 mg/kg in pediatric patients. A Polish guideline on fever management in children noted, "The dosage range was confirmed by a systematic review of clinical studies, which showed that, compared to 10 mg/kg, a dose of 15 mg/kg seems to maintain a lower temperature for a longer time and is more effective in reducing the average temperature compared to baseline values (1.6°C vs. 1.2°C)" [26, 60]. A Japanese guideline for the management of acute otitis media also recommended a range of 10–15 mg/kg oral paracetamol [58].

The 2013 WHO *Pocket Book of Hospital Care for Children* recommends use of weight-based dosing of paracetamol, citing an optimal dose of 10–15 mg/kg for mild pain and fever in infants and children ≥ 2 months of age [8]. The maximum daily dosage is 60 mg/kg/day, with administration every 4 h [26]. Nearly all clinical studies [23, 29, 30, 32, 36–55, 61–70] and guidelines [26, 56–59] captured in the literature search clearly followed weight-based dosing for paracetamol.

4.2 Ibuprofen

Formulations of ibuprofen used in children include tablets, syrups, suspensions, and intravenous formulations [30, 33, 34, 40]. However, as this review describes the use of ibuprofen for self-care, intravenous formulations have not been discussed. Clinical studies [30, 40, 45–47, 49, 50, 53, 54, 63–66, 71–73] and guidelines [56, 57, 59] support weight-based administration for oral ibuprofen in children at a dose of 5–10 mg/kg, with the Polish guideline on fever management recommending a range of 5–10 mg/kg and a maximum daily dosage of 30 mg/kg/day (in children up to 35 kg) or 400 mg every 6 h (in children > 40 kg) [26]. The 2013 WHO *Pocket Book of Hospital Care for Children* recommends use of weight-based dosing of ibuprofen, citing an optimal dose of 5–10 mg/kg for mild pain and 10 mg/kg for fever [8].

Overall, the results of the literature search support weight-based dosing for both paracetamol and ibuprofen in children. A summary of the dosing guidelines retrieved is shown in Table 3.

5 Indications

5.1 Paracetamol

Paracetamol is the first-line treatment for pain and fever in pediatric patients worldwide and the only recommended analgesic for infants between 1 and 3 months of age [8].

Numerous studies were identified that investigated the use of paracetamol in children for a variety of indications, as described below.

The antipyretic effects of paracetamol have been well established in randomized clinical trials [29, 30, 41–43, 49–53, 62, 63, 65, 66, 74, 75]. Treatment with paracetamol reduced dental or tooth extraction pain; > 75% of patients did not require a second dose of analgesic after the first dose of paracetamol at 15 mg/kg [38]. The reported effects of prophylactic administration on post-extraction pain have not been consistent [33, 34, 39, 44, 68, 76]. Findings of representative clinical trials are summarized in Table 2.

A network meta-analysis of randomized controlled trials demonstrated that paracetamol is an effective treatment for migraine in pediatric patients [77]. Guidelines from the American Academy of Neurology (AAN) and the French Society for the Study of Migraine Headache mention paracetamol for the treatment of migraine in children [78, 79]. A blinded, randomized, controlled head-to-head study of paracetamol and ibuprofen in children with migraine found that both drugs achieved similar rates of pain freedom and pain relief, with no differences in tolerability [40].

One randomized, double-blind, placebo-controlled study assessed the effect of a single dose of paracetamol syrup in children 6–12 years of age with pharyngotonsillitis (sore throat) [37]. Patients were randomized 1:1:1 to receive paracetamol syrup 12 mg/kg, open-label ketoprofen lysine salt 40 mg, or double-blind placebo. Greater improvements in sore throat pain over time were observed with paracetamol versus placebo, and improvements with paracetamol were similar to those with ketoprofen lysine salt [37]. Additionally, results from three randomized clinical trials demonstrated the efficacy and tolerability of paracetamol for treating preoperative and/or postoperative tonsillectomy pain [45–47].

Administration of paracetamol as prophylaxis or treatment for vaccine complications has been investigated in several studies [36, 48, 54, 55, 69, 70, 80–84]. Administration of paracetamol following routine vaccinations in children 6 weeks to 9 months of age reduced the incidence of post-vaccination fever compared with placebo [85]. Paracetamol prophylaxis is not recommended for vaccine complications.

Effects of analgesic treatment have been investigated to confirm a lack of interference with vaccine immunogenicity. A study of children 6–47 months of age who received paracetamol to ameliorate fever after administration of an inactivated influenza vaccine showed no evidence of a blunted immune response [81]. Furthermore, a post hoc analysis of a randomized, multicenter study in infants 6–8 weeks of age showed that paracetamol did not affect the immune response to a diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type B combination vaccine, regardless of paracetamol administration timing [86].

Table 3 Summary of dosing guidelines for paracetamol and ibuprofen in pediatric patients [26, 56–58]

Reference	Country/region	Indication	Guidelines
Doria et al. (2021) [56]	Italy	Treatment of fever and acute mild/moderate pain in children	Consensus statements Recommendations for the use of paracetamol and ibuprofen in primary care and emergency settings should overlap The guidelines suggest that the efficacies of paracetamol and ibuprofen are comparable (in terms of efficacy, a 15-mg/kg dose of paracetamol overlaps a 10-mg/kg dose of ibuprofen) Paracetamol showcases a good safety profile when used at the recommended dosage of 15 mg/kg 4 times/day maximum (not to overstep the daily dose of 60 mg/kg; the route of administration and the age of the child are important (e.g., in neonates and infants, the dosage should be adjusted to 12.5 mg/kg every 6 h if given by the IV route) The use of paracetamol is more appropriate in specific conditions: Children at risk of dehydration or dehydrated children and children with varicella, pneumonia, Kawasaki disease, and coagulation disorders (dehydration is a frequent condition in infants with fever)
Green et al. (2021) [57]	Sub-Saharan Africa	Management of acute fever in children	Dosage of antipyretic medication for infants and children > 3 months of age Paracetamol: 15 mg/kg body weight (up to 1 g) every 6 h as necessary (maximum daily dose, 90 mg/kg or 4 g in total) Ibuprofen: 10 mg/kg body weight every 6 h as necessary (maximum daily dose, 40 mg/kg) Both paracetamol and ibuprofen are safe and effective for short-term use in children and are the drugs of choice to manage fever The practices of combining or alternating paracetamol and ibuprofen have limited value and are not recommended Both paracetamol and ibuprofen have been associated with increased risk of bronchospasm in a very small percentage of predisposed children with asthma. Care should be taken when using antipyretic medication for these children The use of NSAIDs has been associated with an elevated risk of severe skin and soft tissue infections in patients with varicella zoster virus infection. Therefore, paracetamol is recommended as the antipyretic of choice in children with chicken pox
Doniec et al. (2021) [26]	Poland	Fever in children	Paracetamol and ibuprofen are antipyretics recommended for use in children Ibuprofen and paracetamol should be administered at stable intervals and not on an as-needed basis at fever detection time; the minimum therapeutic dose should be applied for the shortest time necessary to alleviate the signs and symptoms, and the drugs should not be used for longer than 3 days except in clearly justified situations A switch to another treatment should be considered if the child's condition has not improved A combination of ibuprofen and paracetamol or alternating therapy is not recommended for fever management in children; both drugs should not be administered concomitantly or alternately except in persistent or recurrent anxiety in a child before the next dose Recommended oral regimens: Children < 40 kg Paracetamol: 15 mg/kg every 4 h, maximum 60 mg/kg/day Ibuprofen: 5–10 mg/kg every 6–8 h, maximum 30 mg/kg/day Children > 40–50 kg and 12 years of age Paracetamol: 700–1000 mg every 4–6 h, maximum 4000 mg/day Ibuprofen: 200–400 mg every 4–6 h, maximum 1600 mg/day
Hayashi et al. (2020) [58]	Japan	Management of acute otitis media in children	Paracetamol (10–15 mg/dose) in children with otalgia or fever (≥ 38.5 °C)

IV intravenous, *NSAID* nonsteroidal anti-inflammatory drug

5.2 Ibuprofen

Use of ibuprofen for infants < 3 months of age is not recommended by the WHO, which includes paracetamol as the only recommended analgesic for this population [8]. However, recent studies that directly compared ibuprofen and paracetamol in infants < 3 months of age demonstrated benefits of ibuprofen over paracetamol (e.g., reduced temperature, less pain) [28, 30, 31]. Some treatment guidelines state that both drugs have comparable efficacy but recommend paracetamol over ibuprofen in specific conditions, such as dehydration or risk for dehydration, which often accompanies fever, and in patients with varicella, pneumonia, Kawasaki disease, or coagulation disorders, because of an increased toxicity of ibuprofen compared with paracetamol [56].

Studies were identified that investigated the use of ibuprofen in children for several indications including fever [28, 30, 42, 43, 49, 50, 53, 63–66, 71, 87], dental or tooth extraction pain [33, 34, 44, 76], and migraine [40, 73, 77]. Findings of representative studies are summarized in Table 2. Ibuprofen is also recommended for the treatment of migraine in children in the guidelines of the AAN and the French Society for the Study of Migraine Headache [78, 79].

One study in children with uncomplicated extremity fractures compared the analgesic effect of ibuprofen with that of oral morphine [72]. While both drugs improved pain scores 30 min after administration, treatment with morphine was associated with significantly more adverse effects than treatment with ibuprofen ($p < 0.01$) [72]. The efficacy and tolerability of ibuprofen in the treatment of preoperative and/or postoperative tonsillectomy pain were demonstrated in randomized clinical trials in which paracetamol was a comparator (Table 2) [45–47].

In children immunized with an inactivated influenza vaccine, administration of ibuprofen following vaccination to alleviate fever did not result in a blunted immune response [81]. Prophylactic administration of ibuprofen did not appear to interfere with the immune response to vaccination with pneumococcal conjugate vaccines [36, 88], but it did interfere with the immune response to diphtheria-tetanus-pertussis vaccine (DTaP)/human papilloma virus (HBV)/inactivated polio vaccine (IPV)/*Haemophilus influenzae* type B vaccine (Hib) in a randomized, controlled trial [88]. Lack of interference with the immune response to the pneumococcal conjugated vaccine (*Hemophilus influenzae* protein D-conjugate vaccine [PHiD-CV]) was observed regardless of the timing of prophylactic ibuprofen administration (immediate or delayed during primary or booster vaccination) [89].

6 Paracetamol and Ibuprofen for COVID-19 Symptoms and Post–COVID-19 Immunization Symptoms in Children

As of May 2022, the number of confirmed COVID-19 infections reported by the WHO was over 500 million globally, and rates continue to rise [90]. COVID-19, caused by the severe acute respiratory syndrome coronavirus 2, is associated with a wide array of symptoms, including a spectrum of pulmonary symptoms such as dyspnea (with or without chronic oxygen dependence), fibrotic lung damage, and challenges in discontinuing ventilator use [91, 92]. Patients with COVID-19 infection also display an array of other symptoms. In one outpatient study of patients with COVID-19 infection as defined by WHO criteria ($N = 1487$), the most common symptoms reported were fever and cough (91%), asthenia (60%), body aches/myalgia (57%), headache (55%), dyspnea (32%), chest pain (22%), and ear/nose/throat symptoms such as anosmia (28%), ageusia (28%), and ageusia + anosmia (23%) [93].

The NIH COVID-19 treatment guidelines recommend supportive care for the management of children infected with COVID-19 and for the subset of children who develop multisystem inflammatory syndrome (MIS-C), but they do not specify drugs or regimens. The treatment guidelines also note that individuals infected with COVID-19 who are receiving NSAIDs for an underlying medical condition should not discontinue NSAID therapy unless warranted and that use of paracetamol and NSAIDs for antipyretic therapy should remain similar to that for other patients [94]. The WHO Living Guidance for Clinical Management of COVID-19 (23 November 2021 version) [95] includes a conditional recommendation for the use of corticosteroids in addition to high-quality supportive care for children with MIS-C, referring clinicians to the 2013 WHO *Pocket Book of Hospital Care for Children* [8] for guidance on supportive care management. Consequently, the role of paracetamol and ibuprofen for management of COVID-19 symptoms is not well defined.

COVID-19 is among the top 10 causes of death for children 5–11 years of age, and as of April 15, 2022, the CDC recommends that all individuals ≥ 6 months of age receive a COVID-19 vaccine [96]. The Pfizer-BioNTech mRNA vaccine (COMIRNATY) has received full US Food and Drug Administration approval for use in individuals ≥ 16 years of age [97] and individuals 12–15 years of age, and has emergency use authorization for children 5–11 years of age. The Pfizer-BioNTech vaccine has also received approval from the European Commission for use in individuals ≥ 12 years of age [98]. The Moderna mRNA vaccine, the Johnson & Johnson/Janssen adenoviral vector vaccine, and the

Sinovac-Coronavac inactivated virus vaccine currently have emergency use authorization only for individuals ≥ 18 years of age [99, 100].

The CDC does not recommend the use of analgesics prior to COVID-19 vaccination to prevent side effects. However, paracetamol and NSAIDs may have a role in post-vaccination symptom relief, as the CDC recommends asking the child's healthcare provider for advice on using a non-aspirin analgesic to manage side effects such as injection site pain and swelling, muscle pain, fever, chills, and headache. One publication captured in the literature search suggests the use of paracetamol to treat these symptoms in children [101]. The findings demonstrate that the role of paracetamol and ibuprofen in the management of post–COVID-19 immunization symptoms in children is not well established and will likely continue to evolve as younger children become eligible for vaccination.

7 Discussion

Children experience a wide range of conditions associated with pain and fever. Paracetamol and ibuprofen are used globally in pediatric patients for the treatment of multiple indications involving pain and fever. Clinical studies and guidelines support weight-based dosing of oral paracetamol and ibuprofen in children, with recommended dosages of 10–15 mg/day for paracetamol (maximum of 60 mg/kg/day) and 5–10 mg/kg for ibuprofen (maximum of 30 mg/kg/day in children ≤ 35 kg or 400 mg every 6 h in children > 40 kg). However, no study in pediatric patients could be identified that investigated paracetamol treatment of muscle ache, musculoskeletal pain, or earache (acute otitis media) at the above recommended doses, and only one study investigated paracetamol treatment and ibuprofen for sore throat pain [37]. Similarly, none of the identified studies investigated ibuprofen treatment for acute otitis media pain. Given that parents of children ages 0–18 in GPI-4 most commonly identified sore throat as a pain condition experienced by their children, more studies of paracetamol and ibuprofen in children are needed for this and other pain indications.

Prophylaxis with paracetamol or ibuprofen to manage vaccine reactions is not recommended, as evidence suggests that it is either ineffective [54] or can negatively affect vaccine immunogenicity (e.g., DTaP/HBV/IPV/Hib) [36, 88, 89], depending on the specific vaccine administered. However, paracetamol or ibuprofen use as treatment for reactions to vaccines such as diphtheria, tetanus, pertussis, hepatitis B, and Hib combination does not appear to affect vaccine immunogenicity [81, 86]. Presently, the roles of paracetamol and ibuprofen in COVID-19 infection symptom management and post–COVID-19 vaccination symptom management are not well defined in children and will continue to evolve.

Limitations of this report are typical of those associated with narrative literature reviews and include the subjective nature of the narrative review process and the potential for selection bias of the literature discussed. Although these limitations can be addressed by conducting a systematic literature review, this method was not feasible because of the broad scope of this review. However, we believe that the limitations noted were minimized by following a predefined set of inclusion and exclusion criteria for article selection, as outlined in the "Methods."

8 Conclusion

Accurate, personalized dosing of paracetamol and ibuprofen for selfcare indications is needed for optimal symptom management, as age, weight, and pharmacokinetics can influence dosing approaches in children. Well-designed studies of these medications for the treatment of pain and fever associated with COVID-19 in pediatric patients are urgently needed to ensure optimal relief with minimal toxicity.

Declarations

References

1. Hagen M, Madhavan T, Bell J. Combined analysis of 3 cross-sectional surveys of pain in 14 countries in Europe, the Americas, Australia, and Asia: impact on physical and emotional aspects and quality of life. Scand J Pain. 2020;20(3):575–89. https://doi.org/10.1515/sjpain-2020-0003.

2. Stevens BJ, Zempsky WT. Prevalence and distribution of pain in children. In: Stevens BJ, Hathway G, Zempsky WT, editors. Oxford textbook of pediatric pain. 2nd ed. Oxford: Oxford University Press; 2021.

3. Global Pain Index Report: GSK Consumer Healthcare; 2020. https://www.gsk.com/media/6351/2020-global-plain-index-report.pdf.

4. de Leeuw TG, Dirckx M, Gonzalez Candel A, Scoones GP, Huygen F, de Wildt SN. The use of dipyrone (metamizol) as an analgesic in children: What is the evidence? A review. Paediatr Anaesth. 2017;27(12):1193–201. https://doi.org/10.1111/pan.13257.

5. Ntamabyaliro NY, Burri C, Nzolo DB, Engo AB, Lula YN, Mampunza SM, Nsibu CN, Mesia GK, Kayembe JN, Likwela JL, Kintaudi LM, Tona GL. Drug use in the management of uncomplicated malaria in public health facilities in the Democratic Republic of the Congo. Malar J. 2018;17(1):189. https://doi.org/10.1186/s12936-018-2332-3.

6. Ohashi N, Kohno T. Analgesic effect of acetaminophen: a review of known and novel mechanisms of action. Front Pharmacol. 2020;11:580289. https://doi.org/10.3389/fphar.2020.580289.

7. Przybyła GW, Szychowski KA, Gmiński J. Paracetamol – An old drug with new mechanisms of action. Clin Exp Pharmacol Physiol. 2021;48(1):3–19. https://doi.org/10.1111/1440-1681.13392.

8. World Health Organization. Pocket book of hospital care for children. In: Guidelines for the management of common childhood illnesses. 2nd ed. Geneva, Switzerland: World Health Organization; 2013.

9. van Rensburg R, Reuter H. An overview of analgesics: NSAIDs, paracetamol, and topical analgesics Part 1. S Afr Fam Prac. 2019;61(Suppl 1):S4–10. https://doi.org/10.1080/20786190.2019.1610228.

10. de Martino M, Chiarugi A. Recent advances in pediatric use of oral paracetamol in fever and pain management. Pain Ther. 2015;4(2):149–68. https://doi.org/10.1007/s40122-015-0040-z.

11. Hopkins CS, Underhill S, Booker PD. Pharmacokinetics of paracetamol after cardiac surgery. Arch Dis Child. 1990;65(9):971–6. https://doi.org/10.1136/adc.65.9.971.

12. Prescott LF. Kinetics and metabolism of paracetamol and phenacetin. Br J Clin Pharmacol. 1980;10(Suppl 2):291s-s298.

13. Li J, Chiew AL, Isbister GK, Duffull SB. Sulfate conjugation may be the key to hepatotoxicity in paracetamol overdose. Br J Clin Pharmacol. 2021;87(5):2392–6. https://doi.org/10.1111/bcp.14642.

14. Moriarty C, Carroll W. Paracetamol: pharmacology, prescribing and controversies. Arch Dis Child Educ Pract Ed. 2016;101(6):331–4. https://doi.org/10.1136/archdischild-2014-307287.

15. Anderson BJ, Woollard GA, Holford NH. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. Br J Clin Pharmacol. 2000;50(2):125–34.

16. Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. Anesthesiology. 2002;96(6):1336–45. https://doi.org/10.1097/00000542-200206000-00012.

17. Ji P, Wang Y, Li Z, Doddapaneni S, Hertz S, Furness S, Sahajwalla CG. Regulatory review of acetaminophen clinical pharmacology in young pediatric patients. J Pharm Sci. 2012;101(12):4383–9. https://doi.org/10.1002/jps.23331.

18. Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N. Acetaminophen-induced hepatotoxicity: a comprehensive update. J Clin Transl Hepatol. 2016;4(2):131–42. https://doi.org/10.14218/jcth.2015.00052.

19. Zhao L, Pickering G. Paracetamol metabolism and related genetic differences. Drug Metab Rev. 2011;43(1):41–52. https://doi.org/10.3109/03602532.2010.527984.

20. Piana C, Danhof M, Della PO. Influence of covariate distribution on the predictive performance of pharmacokinetic models in paediatric research. Br J Clin Pharmacol. 2014;78(1):145–57. https://doi.org/10.1111/bcp.12322.

21. Cella M, Knibbe C, Danhof M, Della PO. What is the right dose for children? Br J Clin Pharmacol. 2010;70(4):597–603. https://doi.org/10.1111/j.1365-2125.2009.03591.x.

22. Burton ZA, Lewis R, Bennett T, Lewis H, Heikal S, Selman A, Sinha D, McLernon DJ, Engelhardt T, Brooks P, Edwards M, Paediatric Anaesthesia Trainee Research Network. Perioperative paracetamol prescribing in obese versus normal weight children in the UK: a national prospective multicentre observational cohort study abstract. Anesth Analg. 2021;133(3(Suppl 2)):1194–5. https://doi.org/10.1213/01.ane.0000791544.44545.82.

23. Husain N, Wadwa A, Christiansen N. Evaluation of analgesic doses prescribed postoperatively for overweight and obese children [abstract P20]. Arch Dis Child. 2020;105(9):e16–7. https://doi.org/10.1136/archdischild-2020-NPPG.29.

24. Zempsky WT, Bhagat PK, Siddiqui K. Practical challenges-use of paracetamol in children and youth who are overweight or obese: a narrative review. Paediatr Drugs. 2020;22(5):525–34. https://doi.org/10.1007/s40272-020-00417-z.

25. Kauffman RE, Nelson MV. Effect of age on ibuprofen pharmacokinetics and antipyretic response. J Pediatr. 1992;121(6):969–73. https://doi.org/10.1016/s0022-3476(05)80354-3.

26. Doniec Z, Jackowska T, Sybilski A, Woroń J, Mastalerz-Migas A. FEVER in children – recommendations for primary care doctors—FEVER COMPASS. Fam Med Prim Care Rev. 2021;23(1):99–115. https://doi.org/10.5114/fmpcr.2021.102648.

27. Anderson BJ, Hannam JA. A target concentration strategy to determine ibuprofen dosing in children. Paediatr Anaesth. 2019;29(11):1107–13. https://doi.org/10.1111/pan.13731.

28. Tan E, Braithwaite I, McKinlay CJD, Dalziel SR. Comparison of acetaminophen (paracetamol) with ibuprofen for treatment of fever or pain in children younger than 2 years: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(10):e2022398. https://doi.org/10.1001/jamanetworkopen.2020.22398.

29. Okereke B, Ibeleme O, Bisi-Onyemaechi A. Randomised comparative trial of the efficacy of paracetamol syrup and dispersible tablets for the treatment of fever in children. J Int Med Res. 2021;49(3):300060521999755. https://doi.org/10.1177/0300060521999755.

30. Alaje EO, Udoh EE, Akande PA, Odey FA, Meremikwu MM. Ibuprofen versus paracetamol for treating fever in preschool children in Nigeria: a randomized clinical trial of effectiveness and safety. Pan Afr Med J. 2020;36:350. https://doi.org/10.11604/pamj.2020.36.350.21393.

31. Paul IM, Walson PD. Acetaminophen and ibuprofen in the treatment of pediatric fever: a narrative review. Curr Med Res Opin. 2021;37(8):1363–75. https://doi.org/10.1080/03007995.2021.1928617.

32. Poonai N, Kumar K, Coriolano K, Thompson G, Brahmbhatt S, Dzongowski E, Stevens H, Gupta P, Miller M, Elsie S, Ashok D, Joubert G, Lim R, Bütter A, Ali S. Hyoscine butylbromide versus acetaminophen for nonspecific colicky abdominal pain in children: a randomized controlled trial. CMAJ. 2020;192(48):e1612–9. https://doi.org/10.1503/cmaj.201055.

33. Raslan N, Zouzou T. Comparison of preemptive ibuprofen, acetaminophen, and placebo administration in reducing peri- and postoperative pain in primary tooth extraction: a randomized clinical trial. Clin Exp Dent Res. 2021;7(6):1045–52. https://doi.org/10.1002/cre2.465.

34. Santos PS, Massignan C, de Oliveira EV, Miranda Santana C, Bolan M, Cardoso M. Does the pre-emptive administration of paracetamol or ibuprofen reduce trans- and post-operative pain in primary molar extraction? A randomized placebo-controlled clinical trial. Int J Paediatr Dent. 2020;30(6):782–90. https://doi.org/10.1111/ipd.12649.

35. van Uum RT, Venekamp RP, Zuithoff NP, Sjoukes A, van de Pol AC, Schilder AG, Damoiseaux RA. Improving pain management in childhood acute otitis media in general practice: a cluster randomised controlled trial of a GP-targeted educational intervention. Br J Gen Pract. 2020;70(699):e684–95. https://doi.org/10.3399/bjgp20X712589.

36. Koufoglou E, Kourlaba G, Michos A. Effect of prophylactic administration of antipyretics on the immune response to pneumococcal conjugate vaccines in children: a systematic review. Pneumonia (Nathan Qld). 2021;13(1):7. https://doi.org/10.1186/s41479-021-00085-8.

37. Ruperto N, Carozzino L, Jamone R, Freschi F, Picollo G, Zera M, Della Casa Alberighi O, Salvatori E, Del Vecchio A, Dionisio P, Martini A. A randomized, double-blind, placebo-controlled trial of paracetamol and ketoprofen lysine salt for pain control in children with pharyngotonsillitis cared by family pediatricians. Ital J Pediatr. 2011;37:48. https://doi.org/10.1186/1824-7288-37-48.

38. Baillargeau C, Lopez-Cazaux S, Charles H, Ordureau A, Dajean-Trutaud S, Prud'homme T, Hyon I, Soueidan A, Alliot-Licht B, Renard E. Post-operative discomforts in children after extraction of primary teeth. Clin Exp Dent Res. 2020;6(6):650–8. https://doi.org/10.1002/cre2.316.

39. Fux-Noy A, Bendahan Y, Ungar E, Shmueli A, Halperson E, Ram D, Moskovitz M. Does preoperative paracetamol reduce pain after dental treatment? A randomized controlled double-blind study. Quintessence Int. 2020;51(9):732–40. https://doi.org/10.3290/j.qi.a45101.

40. Pavithra V, Mishra D, Behera S, Juneja M. Paracetamol versus ibuprofen for the acute treatment of migraine headache in children: a blinded randomized controlled trial. Indian J Pediatr. 2020;87(10):781–6. https://doi.org/10.1007/s12098-020-03315-x.

41. Senel S, Erkek N, Karacan CD. Comparison of acetaminophen and ketoprofen in febrile children: a single dose randomized clinical trial. Indian J Pediatr. 2012;79(2):213–7. https://doi.org/10.1007/s12098-011-0500-3.

42. Kokki H, Kokki M. Ketoprofen versus paracetamol (acetaminophen) or ibuprofen in the management of fever: results of two randomized, double-blind, double-dummy, parallel-group, repeated-dose, multicentre, phase III studies in children. Clin

43. Jayawardena S, Kellstein D. Antipyretic efficacy and safety of ibuprofen versus acetaminophen suspension in febrile children: results of 2 randomized, double-blind, single-dose studies. Clin Pediatr (Phila). 2017;56(12):1120–7.

44. Kharouba J, Ratson T, Somri M, Blumer S. Preemptive analgesia by paracetamol, ibuprofen or placebo in pediatric dental care: a randomized controlled study. J Clin Pediatr Dent. 2019;43(1):51–5. https://doi.org/10.17796/1053-4625-43.1.10.

45. Mahgoobifard M, Mirmesdagh Y, Imani F, Najafi A, Nataj-Majd M. The analgesic efficacy of preoperative oral Ibuprofen and acetaminophen in children undergoing adenotonsillectomy: a randomized clinical trial. Anesth Pain Med. 2014;4(1):e15049. https://doi.org/10.5812/aapm.15049.

46. Mirashrafi F, Tavakolnejad F, Amirzargar B, Abasi A, Amali A. Effect of paracetamol versus ibuprofen in adenotonsillectomy. Iran J Otorhinolaryngol. 2021;33(119):355–9. https://doi.org/10.22038/ijorl.2021.56501.2945.

47. Jotić A, Savić Vujović K, Milovanović J, Vujović A, Radin Z, Milić N, Vučković S, Medić B, Prostran M. Pain management after surgical tonsillectomy: is there a favorable analgesic? Ear Nose Throat J. 2019;98(6):356–61. https://doi.org/10.1177/0145561319846065.

48. Karambin MM, Heidarzadeh A, Sharghy R, Dalili S, Hashemian H. Effects of administering prophylactic acetaminophen on short-term complications of vaccination in 6-month-old infants. Int J Prev Med. 2015;6:124. https://doi.org/10.4103/2008-7802.172380.

49. Paul IM, Sturgis SA, Yang C, Engle L, Watts H, Berlin CM Jr. Efficacy of standard doses of ibuprofen alone, alternating, and combined with acetaminophen for the treatment of febrile children. Clin Ther. 2010;32(14):2433–40. https://doi.org/10.1016/j.clinthera.2011.01.006.

50. Kramer LC, Richards PA, Thompson AM, Harper DP, Fairchok MP. Alternating antipyretics: antipyretic efficacy of acetaminophen versus acetaminophen alternated with ibuprofen in children. Clin Pediatr (Phila). 2008;47(9):907–11. https://doi.org/10.1177/0009922808319967.

51. Hay AD, Costelloe C, Redmond NM, Montgomery AA, Fletcher M, Hollinghurst S, Peters TJ. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. BMJ. 2008;337:a1302. https://doi.org/10.1136/bmj.a1302.

52. Friedman AD, Barton LL. Efficacy of sponging vs acetaminophen for reduction of fever. Sponging Study Group. Pediatr Emerg Care. 1990;6(1):6–7. https://doi.org/10.1097/00006565-199003000-00003.

53. Walson PD. Ibuprofen versus paracetamol for the treatment of fever in children. Br J Clin Pract Suppl. 1990;70:19–21.

54. Jackson LA, Dunstan M, Starkovich P, Dunn J, Yu O, Nelson JC, Rees T, Zavitkovsky A. Prophylaxis with acetaminophen or ibuprofen for prevention of local reactions to the fifth diphtheria-tetanus toxoids-acellular pertussis vaccination: a randomized, controlled trial. Pediatrics. 2006;117(3):620–5. https://doi.org/10.1542/peds.2005-1217.

55. Ipp MM, Gold R, Greenberg S, Goldbach M, Kupfert BB, Lloyd DD, Maresky DC, Saunders N, Wise SA. Acetaminophen prophylaxis of adverse reactions following vaccination of infants with diphtheria-pertussis-tetanus toxoids-polio vaccine. Pediatr Infect Dis J. 1987;6(8):721–5. https://doi.org/10.1097/00006454-198708000-00005.

56. Doria M, Careddu D, Iorio R, Verrotti A, Chiappini E, Barbero GM, Ceschin F, Dell'Era L, Fabiano V, Mencacci M, Carlomagno F, Libranti M, Mazzone T, Vitale A. Paracetamol and ibuprofen in the treatment of fever and acute mild-moderate

Drug Investig. 2010;30(6):375–86. https://doi.org/10.2165/11534930-000000000-00000.

pain in children: Italian experts' consensus statements. Children (Basel). 2021. https://doi.org/10.3390/children8100873.

57. Green R, Webb D, Jeena PM, Wells M, Butt N, Hangoma JM, Moodley RS, Maimin J, Wibbelink M, Mustafa F. Management of acute fever in children: consensus recommendations for community and primary healthcare providers in sub-Saharan Africa. Afr J Emerg Med. 2021;11(2):283–96. https://doi.org/10.1016/j.afjem.2020.11.004.

58. Hayashi T, Kitamura K, Hashimoto S, Hotomi M, Kojima H, Kudo F, Maruyama Y, Sawada S, Taiji H, Takahashi G, Takahashi H, Uno Y, Yano H. Clinical practice guidelines for the diagnosis and management of acute otitis media in children-2018 update. Auris Nasus Larynx. 2020;47(4):493–526. https://doi.org/10.1016/j.anl.2020.05.019.

59. Sullivan JE, Farrar HC. Fever and antipyretic use in children. Pediatrics. 2011;127(3):580–7. https://doi.org/10.1542/peds.2010-3852.

60. Temple AR, Temple BR, Kuffner EK. Dosing and antipyretic efficacy of oral acetaminophen in children. Clin Ther. 2013;35(9):1361-75.e1-45. https://doi.org/10.1016/j.clinthera.2013.06.022.

61. Motov S, Butt M, Masoudi A, Palacios W, Fassassi C, Drapkin J, Likourezos A, Hossain R, Brady J, Rothberger N, Flom P, Zerzan J, Marshall J. Comparison of oral ibuprofen and acetaminophen with either analgesic alone for pediatric emergency department patients with acute pain. J Emerg Med. 2020;58(5):725–32. https://doi.org/10.1016/j.jemermed.2020.02.010.

62. Thomas S, Vijaykumar C, Naik R, Moses PD, Antonisamy B. Comparative effectiveness of tepid sponging and antipyretic drug versus only antipyretic drug in the management of fever among children: a randomized controlled trial. Indian Pediatr. 2009;46(2):133–6.

63. Wong A, Sibbald A, Ferrero F, Plager M, Santolaya ME, Escobar AM, Campos S, Barragan S, De Leon GM, Kesselring GL. Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study. Clin Pediatr (Phila). 2001;40(6):313–24. https://doi.org/10.1177/000992280104000602.

64. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. Pediatrics. 1999;104(4):e39.

65. Vauzelle-Kervroedan F, d'Athis P, Pariente-Khayat A, Debregeas S, Olive G, Pons G. Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children. J Pediatr. 1997;131(5):683–7.

66. Sidler J, Frey B, Baerlocher K. A double-blind comparison of ibuprofen and paracetamol in juvenile pyrexia. Br J Clin Pract Suppl. 1990;70:22–5.

67. Thompson J, Fleet W, Lawrence E, Pierce E, Morris L, Wright P. A comparison of acetaminophen and rimantadine in the treatment of influenza A infection in children. J Med Virol. 1987;21(3):249–55. https://doi.org/10.1002/jmv.1890210308.

68. O'Donnell A, Henderson M, Fearne J, O'Donnell D. Management of postoperative pain in children following extractions of primary teeth under general anaesthesia: a comparison of paracetamol, Voltarol and no analgesia. Int J Paediatr Dent. 2007;17(2):110–5. https://doi.org/10.1111/j.1365-263X.2006.00800.x.

69. Uhari M, Hietala J, Viljanen MK. Effect of prophylactic acetaminophen administration on reaction to DTP vaccination. Acta Paediatr Scand. 1988;77(5):747–51. https://doi.org/10.1111/j.1651-2227.1988.tb10741.x.

70. Prymula R, Siegrist CA, Chlibek R, Zemlickova H, Vackova M, Smetana J, Lommel P, Kaliskova E, Borys D, Schuerman L. 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. https://doi.org/10.1016/s0140-6736(09)61208-3.

71. Magni AM, Scheffer DK, Bruniera P. Antipyretic effect of ibuprofen and dipyrone in febrile children. J Pediatr (Rio J). 2011;87(1):36–42. https://doi.org/10.2223/jped.2060.

72. Poonai N, Bhullar G, Lin K, Papini A, Mainprize D, Howard J, Teefy J, Bale M, Langford C, Lim R, Stitt L, Rieder MJ, Ali S. Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. CMAJ. 2014;186(18):1358–63. https://doi.org/10.1503/cmaj.140907.

73. Dooley JM, Gordon KE, Wood EP, Brna PM, MacSween J, Fraser A. Caffeine as an adjuvant to ibuprofen in treating childhood headaches. Pediatr Neurol. 2007;37(1):42–6. https://doi.org/10.1016/j.pediatrneurol.2007.02.016.

74. Kinmonth AL, Fulton Y, Campbell MJ. Management of feverish children at home. BMJ. 1992;305(6862):1134–6. https://doi.org/10.1136/bmj.305.6862.1134.

75. Kramer MS, Naimark LE, Roberts-Bräuer R, McDougall A, Leduc DG. Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin. Lancet. 1991;337(8741):591–4. https://doi.org/10.1016/0140-6736(91)91648-e.

76. Baygin O, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. Int J Paediatr Dent. 2011;21(4):306–13. https://doi.org/10.1111/j.1365-263X.2011.01124.x.

77. Wang G, Tan T, Liu Y, Hong P. Drugs for acute attack of pediatric migraine: a network meta-analysis of randomized controlled trials. Clin Neurol Neurosurg. 2020;195:105853. https://doi.org/10.1016/j.clineuro.2020.105853.

78. Oskoui M, Pringsheim T, Holler-Managan Y, Potrebic S, Billinghurst L, Gloss D, Hershey AD, Licking N, Sowell M, Victorio MC, Gersz EM, Leininger E, Zanitsch H, Yonker M, Mack K. Practice guideline update summary: acute treatment of migraine in children and adolescents: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2019;93(11):487–99. https://doi.org/10.1212/wnl.0000000000008095.

79. Lanteri-Minet M, Valade D, Geraud G, Lucas C, Donnet A. Revised French guidelines for the diagnosis and management of migraine in adults and children. J Headache Pain. 2014;15(1):2. https://doi.org/10.1186/1129-2377-15-2.

80. Dolhain J, Janssens W, Dindore V, Mihalyi A. Infant vaccine co-administration: review of 18 years of experience with GSK's hexavalent vaccine co-administered with routine childhood vaccines. Expert Rev Vaccines. 2020;19(5):419–43. https://doi.org/10.1080/14760584.2020.1758560.

81. Walter EB, Hornik CP, Grohskopf L, McGee CE, Todd CA, Museru OI, Harrington L, Broder KR. The effect of antipyretics on immune response and fever following receipt of inactivated influenza vaccine in young children. Vaccine. 2017;35(48 Pt B):6664–71. https://doi.org/10.1016/j.vaccine.2017.10.020.

82. Hayat H, Khan PS, Hayat G. The effect of prophylactic paracetamol administration on adverse reactions following DTP vaccination. Eastern J Med. 2011;16:258–60.

83. Prymula R, Esposito S, Zuccotti GV, Xie F, Toneatto D, Kohl I, Dull PM. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine (I). Hum Vaccin Immunother. 2014;10(7):1993–2004. https://doi.org/10.4161/hv.28666.

84. Lewis K, Cherry JD, Sachs MH, Woo DB, Hamilton RC, Tarle JM, Overturf GD. The effect of prophylactic acetaminophen

administration on reactions to DTP vaccination. Am J Dis Child. 1988;142(1):62–5. https://doi.org/10.1001/archpedi.1988.02150010072025.

85. Jackson LA, Peterson D, Dunn J, Hambidge SJ, Dunstan M, Starkovich P, Yu O, Benoit J, Dominguez-Islas CP, Carste B, Benson P, Nelson JC. A randomized placebo-controlled trial of acetaminophen for prevention of post-vaccination fever in infants. PLoS ONE. 2011;6(6):e20102. https://doi.org/10.1371/journal.pone.0020102.

86. Sil A, Ravi MD, Patnaik BN, Dhingra MS, Dupuy M, Gandhi DJ, Dhaded SM, Dubey AP, Kundu R, Lalwani SK, Chhatwal J, Mathew LG, Gupta M, Sharma SD, Bavdekar SB, Rout SP, Jayanth MV, D'Cor NA, Mangarule SA, Ravinuthala S, Reddy EJ. Effect of prophylactic or therapeutic administration of paracetamol on immune response to DTwP-HepB-Hib combination vaccine in Indian infants. Vaccine. 2017;35(22):2999–3006. https://doi.org/10.1016/j.vaccine.2017.03.009.

87. Kloeden B, Tham D, Oakley E, Cheek J. Community use of paracetamol and ibuprofen in children with fever. J Paediatr Child Health. 2021;57(10):1640–4. https://doi.org/10.1111/jpc.15580.

88. Wysocki J, Center KJ, Brzostek J, Majda-Stanislawska E, Szymanski H, Szenborn L, Czajka H, Hasiec B, Dziduch J, Jackowska T, Witor A, Kopińska E, Konior R, Giardina PC, Sundaraiyer V, Patterson S, Gruber WC, Scott DA, Gurtman A. A randomized study of fever prophylaxis and the immunogenicity of routine pediatric vaccinations. Vaccine. 2017;35(15):1926–35. https://doi.org/10.1016/j.vaccine.2017.02.035.

89. Falup-Pecurariu O, Man SC, Neamtu ML, Chicin G, Baciu G, Pitic C, Cara AC, Neculau AE, Burlea M, Brinza IL, Schnell CN, Sas V, Lupu VV, François N, Swinnen K, Borys D. Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: an open-label, randomized, controlled, non-inferiority trial. Hum Vaccin Immunother. 2017;13(3):649–60. https://doi.org/10.1080/21645515.2016.1223001.

90. Coronavirus disease (COVID-19) pandemic: World Health Organization; 2021 [2021]. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 16 Feb 2023.

91. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52(11):549–57. https://doi.org/10.1152/physiolgenomics.00089.2020.

92. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N, Bikdeli B, Dietz D, Der-Nigoghossian C, Liyanage-Don N, Rosner GF, Bernstein EJ, Mohan S, Beckley AA, Seres DS, Choueiri TK, Uriel N, Ausiello JC, Accili D, Freedberg DE, Baldwin M, Schwartz A, Brodie D, Garcia CK, Elkind MSV, Connors JM, Bilezikian JP, Landry DW, Wan EY. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601–15. https://doi.org/10.1038/s41591-021-01283-z.

93. Lapostolle F, Schneider E, Vianu I, Dollet G, Roche B, Berdah J, Michel J, Goix L, Chanzy E, Petrovic T, Adnet F. Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study. Intern Emerg Med. 2020;15(5):813–7. https://doi.org/10.1007/s11739-020-02379-z.

94. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Institutes of Health; 2021 [October 22, 2021]. https://www.covid19treatmentguidelines.nih.gov/. Accessed 16 Feb 2023.

95. COVID-19 clinical management. Living guidance: World Health Organization; 2021 [January 25, 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/338882/WHO-2019-nCoV-clinical-2021.1-eng.pdf?sequence=1&isAllowed=y. Accessed 16 Feb 2023.

96. COVID-19 vaccines for children and teens: Centers for Disease Control and Prevention; 2021 [November 23, 2021]. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/children-teens.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fvaccines%2Frecommendations%2Fadolescents.html. Accessed 16 Feb 2023.

97. Comirnaty [package insert]. Mainz, Germany: BioNTech Manufacturing GmbH; 2021 August 2021.

98. Comirnaty [summary of product characteristics]. Mainz, Germany: BioNTech Manufacturing GmbH; 2021 November 2021.

99. Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19): Moderna; 2022 [January 31, 2022]. https://www.fda.gov/media/144637/download. Accessed 16 Feb 2023.

100. Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) Emergency Use Authorization (EUA) of the Janssen COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19): Janssen; 2022 [January 31, 2022]. https://www.janssenlabels.com/emergency-use-authorization/Janssen+COVID-19+Vaccine-HCP-fact-sheet.pdf. Accessed 16 Feb 2023.

101. Thompson LA, Rasmussen SA. Children and COVID-19 vaccines. JAMA Pediatr. 2021;175(8):876. https://doi.org/10.1001/jamapediatrics.2021.1974.

102. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Lower limb pain in a preadolescent population: prognosis and risk factors for chronicity–a prospective 1- and 4-year follow-up study. Pediatrics. 2005;116(3):673–81. https://doi.org/10.1542/peds.2004-1758.

103. Southey ER, Soares-Weiser K, Kleijnen J. Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. Curr Med Res Opin. 2009;25(9):2207–22. https://doi.org/10.1185/03007990903116255.

104. Yin F, Liu Y, Guo H. Comparison between ibuprofen and acetaminophen in the treatment of infectious fever in children: a meta-analysis. J Healthc Eng. 2022;2022:1794258. https://doi.org/10.1155/2022/1794258.

105. Bird SE, Williams K, Kula K. Preoperative acetaminophen vs ibuprofen for control of pain after orthodontic separator placement. Am J Orthod Dentofacial Orthop. 2007;132(4):504–10. https://doi.org/10.1016/j.ajodo.2006.11.019.

106. Primosch RE, Nichols DL, Courts FJ. Comparison of preoperative ibuprofen, acetaminophen, and placebo administration on the parental report of postextraction pain in children. Pediatr Dent. 1995;17(3):187–91.

107. Cuvellier JC, Donnet A, Guégan-Massardier E, Nachit-Ouinekh F, Parain D, Vallée L. Treatment of primary headache in children: a multicenter hospital-based study in France. J Headache Pain. 2009;10(6):447–53. https://doi.org/10.1007/s10194-009-0158-7.

108. Silver S, Gano D, Gerretsen P. Acute treatment of paediatric migraine: a meta-analysis of efficacy. J Paediatr Child Health. 2008;44(1–2):3–9. https://doi.org/10.1111/j.1440-1754.2007.01206.x.

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