GRHTA
Glob Reg Health Technol Assess 2025; 12: 227-233
ISSN 2283-5733 | DOI: 10.33393/grhta.2025.3579
ORIGINAL RESEARCH ARTICLE
Open Access

Optimising pediatric paracetamol and ibuprofen use: a retrospective study with expert evaluation of efficacy, safety, and healthcare costs

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ABSTRACT

Background: Paracetamol and ibuprofen are widely used for fever and pain in children, but real-world prescribing often deviates from guidelines, leading to potentially avoidable complications and healthcare costs.
Objectives: To estimate the clinical and economic burden associated with inappropriate use of paracetamol and ibuprofen in Italian pediatric care and to identify high-risk clinical scenarios in which safer prescribing may reduce complications.
Methods: A retrospective analysis was conducted on national hospital discharge records (2010-2016), focusing on DRGs and ICD-9-CM codes linked to adverse events following antipyretic or NSAID use in children aged 0-17. A qualitative assessment was also carried out through expert consultation to contextualize findings.
Results: Among 999,739 hospital discharges, 4,308 cases (0.43%) developed complications within three years. ENT procedures and renal diagnoses showed the highest complication rates and costs. Children under three accounted for the largest share of healthcare expenditure. A scenario analysis using pneumonia data suggested that up to 3,000 complications and €10 million in costs could be avoided with more selective NSAID use. Experts recommended prioritizing paracetamol in high-risk scenarios, including dehydration, respiratory infections, and varicella.
Conclusions: Inappropriate use of antipyretics in pediatric care is associated with a measurable clinical and financial burden. Greater adherence to prescribing recommendations, especially in vulnerable populations, can improve outcomes and reduce costs. Educating caregivers and harmonizing clinical practices are key priorities.

Keywords: Adverse drug reactions, Health economics, Ibuprofen, Paracetamol, Pediatrics

Introduction

Paracetamol and ibuprofen are widely recommended in both national and international paediatric guidelines for the symptomatic management of fever and pain. While both active substances are recognised as first-line options, current recommendations emphasize a tailored approach based on clinical context to minimize avoidable adverse events (1-4). Drug selection should therefore consider specific criteria such as patient age and the presence of comorbidities (5-7).

Received: June 9, 2025
Accepted: September 14, 2025
Published online: October 7, 2025

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Despite well-established evidence and existing clinical guidelines, inappropriate use of drugs for fever and pain management remains common in pediatric practice (8-10), exposing patients to risks such as prolonged symptom duration or the onset of complications linked to adverse drug reactions (6,11-13). A 2021 systematic review found that 56% of international guidelines explicitly favor paracetamol over ibuprofen; although both agents are effective in temperature control, ibuprofen is generally discouraged in children with risk of dehydration or underlying medical conditions (14). Paracetamol is frequently preferred due to its more favorable safety profile, while ibuprofen is indicated in the presence of significant inflammatory processes (5-7,14). Although paracetamol is generally considered safer and widely recommended as first-line therapy, its misuse is not risk-free. In pediatric settings, errors in administration and unintentional overdosing are causes of intoxication, with hepatotoxicity representing the most serious outcome; reported clinical

manifestations include gastrointestinal symptoms (nausea, vomiting), biochemical evidence of liver injury such as hypertransaminasemia, and, in severe cases, acute liver failure as documented by pharmacovigilance and poison-control data (15-16). Adverse effects related to ibuprofen use, particularly when the drug is taken for extended periods or outside clinical indications, have been consistently reported in pediatric cohorts and pharmacovigilance analyses. These include renal dysfunction and gastrointestinal complications; signals of infection-related worsening have also been reported in selected contexts, particularly in febrile, dehydrated children (13-16). A national survey conducted in 2020 among 181 Italian pediatricians documented 191 cases of adverse reactions, with gastrointestinal complaints—such as epigastric pain, nausea, and bleeding—being the most frequently reported. In fewer cases, physicians observed kidney-related issues or complicated infections like empyema. In approximately 28% of these cases, the underlying cause was incorrect dosing, excessive treatment duration, or inappropriate dosing intervals (17). Although ibuprofen is still generally viewed as safe when used appropriately, according to Italian Medicines Agency (AIFA) pharmacovigilance reports—as summarised by Quaglietta et al.—reports of suspected ibuprofen-related adverse drug reactions in children have increased since 2010, in parallel with wider over-the-counter use (18). Against this background—and in light of regulatory and epidemiological signals specifically concerning ibuprofen in vulnerable children—the present analysis focuses on ibuprofen-related contexts when examining complications captured in administrative data, while acknowledging that inappropriate use of both drugs can be harmful.

Consistent with prior guidance and observational evidence (12,15,19,20-30), clinical contexts in which paracetamol is generally preferred include:

- Infants under 3 months: Observational data suggest that paracetamol has shown better tolerability compared to ibuprofen in treating patent ductus arteriosus, with fewer renal and gastrointestinal complications (12,19,20);
- Dehydration: Favored because of its lower impact on kidney function (12,14,20,21);
- Respiratory infections: Paracetamol is often preferred to reduce potential risks in selected scenarios; however, evidence remains heterogeneous(12,22-27);
- Urinary tract infections: Often selected to minimize potential adverse outcomes (26);
- Varicella: Paracetamol is commonly chosen given concerns about severe secondary skin/soft-tissue infections reported with NSAIDs (12,20,28,29);
- Post-operative pain: Considered safer due to a reduced incidence of gastrointestinal side effects (5,12).

At home, it is not uncommon for caregivers to alternate or combine paracetamol and ibuprofen, often without medical guidance. According to a 2025 review, this practice is followed by more than 20% of parents. Previous reviews also note that alternating or combining paracetamol and ibuprofen is generally considered only after monotherapy failure, and should be guided by clinical assessment (20). In parallel, nearly 68% believe fever itself is inherently dangerous—an attitude that can drive unnecessary or excessive use of medications intended for fever control (30).

Such patterns raise concern. Unsupervised administration may lead to timing errors, dosing overlaps, or overuse. While paracetamol overdoses are more frequently reported in self-medication scenarios, ibuprofen has been more often linked to clinically significant complications, particularly in febrile children who are dehydrated or in the early phase of viral illness (16). Although these associations do not prove causality, they highlight the importance of appropriate clinical evaluation before starting treatment, and of clear communication with families about when and how to intervene.

The consequences of suboptimal prescribing are not only clinical. Inappropriate use of these drugs can also strain healthcare resources. The 2022 OSMED report shows that, over the last seven years, the use of fever and pain medications in Italy increased markedly—from 16.2 to 25 DDD/1,000 inhabitants/day—with a 20% jump in just one year (31). Paracetamol remains the most widely used agent in terms of both spending (€7.01 per capita) and consumption (11.1 DDD/1,000 inhabitants/day), followed by ibuprofen (4.1 DDD/1,000 inhabitants/day), which accounts for over half of all NSAID prescriptions. Of note, ibuprofen also has the highest cost per day of therapy (€2.89), suggesting that its misuse, when it occurs, may have a disproportionately high economic impact on the national health system.

Considering the context outlined above, encouraging the appropriate use of paracetamol and ibuprofen in children emerges as a strategic priority—not only to improve clinical outcomes and reduce preventable complications, but also to support a more efficient and sustainable use of healthcare resources.

This analysis aims to estimate the potential clinical and economic burden linked to inappropriate prescribing of these therapies in pediatric settings. The analysis is based on Diagnosis-Related Groups (DRGs) associated with adverse events and includes a case study illustrating the possible impact in terms of both health outcomes and costs.

Methods

The study was structured in two phases:

- A retrospective analysis of administrative healthcare data, aimed at estimating the costs associated with the use of paracetamol and ibuprofen in pediatric patients, with a specific focus on adverse events (AEs) and potentially avoidable hospital admissions linked to inappropriate use.
- A qualitative assessment was conducted through consultation with a multidisciplinary panel of key opinion leaders (KOLs) to identify and validate best practices for the pharmacological management of fever and pain in specific pediatric scenarios.

Administrative Data Analysis

Data source

The analysis was based on data from the national Hospital Discharge Records (SDO) system, which collects information

on all inpatient and day-hospital admissions from public and accredited private facilities within the Italian National Health Service (NHS). This database includes demographic, clinical, and administrative details for each patient, with diagnoses and procedures coded using the ICD-9-CM classification system. Cross-country comparability with ICD-10–based systems is limited. To mitigate this, we report the full code lists and outcome definitions in Tables 1-2 and, where possible, use aggregated clinical categories to minimize coding-system artefacts.

The dataset covers the period from January 1, 2010, to December 31, 2016.

We pre-specified pediatric DRGs to capture complications plausibly related to inappropriate antipyretic use, based on three criteria: (i) biological plausibility (e.g., ENT surgery and upper-airway conditions; lower-respiratory infections; bronchitis/asthma; kidney and urinary tract diagnoses); (ii) frequency and clinical relevance in the 0–17 age groups; and (iii) coding reliability in administrative data. The DRG list and the corresponding ICD-9-CM outcome codes (e.g., pleural empyema, retropharyngeal abscess, acute renal failure, mastoiditis, post-operative hemorrhage) are reported in Tables 1-2. We considered all acute ordinary admissions with one of the DRGs listed in Table 1.

Patients were then followed for three years after discharge from the index hospitalization to monitor for the occurrence of relevant clinical complications. These were identified through the presence of subsequent acute admissions with a principal diagnosis corresponding to one of the ICD-9-CM codes shown in Table 2. In the absence of clinical chart validation, this strategy may overestimate associations because of residual confounding and outcome misclassification. Accordingly, findings are interpreted as observational associations rather than causal effects.

TABLE 1 - DRG codes included in the analysis

Code	Description
060	Tonsillectomy and/or adenoidectomy, age <18 years
070	Otitis media and upper respiratory infections, age <18 years
081	Respiratory infections and inflammations, age <18 years
091	Simple pneumonia and pleuritis, age <18 years
098	Bronchitis and asthma, age <18 years
141	Syncope and collapse with complications or comorbidities (CC)

TABLE 2 - ICD-9-CM codes for adverse event monitoring

Code	Description
510-510.9	Pleural empyema
478.24	Retropharyngeal abscess
584.9	Acute renal failure
593.89	Tubulopathy
052.1	Skin infection (post-varicella)
383.0	Acute mastoiditis
383.2	Other mastoiditis and related conditions
478.1	Post-tonsillectomy hemorrhage
478.2	Post-adenoidectomy hemorrhage
518.1	Other non-specified post-operative bleeding
998.11	Post-operative hemorrhage, unspecified

The descriptive analysis made it possible to estimate the proportion of patients who developed complications, the total number of complication-related hospitalizations, and the corresponding financial impact for the National Health Service—both overall and on a per-patient basis.

This analysis used fully anonymized administrative data collected for routine care. According to national regulations and institutional policy, formal ethics committee approval and informed consent were not required. The analysis complied with the Declaration of Helsinki and applicable data-protection regulations.

Expert Panel

A group of experts was engaged based on their recognized experience in pediatric pharmacology, health economics, and clinical practice. The panel included a clinical pharmacologist, a health economist, a hospital-based pediatrician, and a community pediatrician.

Structured meetings were held to guide the discussion, with the goal of identifying—starting from a review of the available literature—key concerns surrounding the use of fever and anti-inflammatory medications in children. Particular attention was paid to scenarios in which inappropriate use may increase the risk of complications.

Following the meetings, experts were asked to complete a structured questionnaire designed to collect additional inputs on:

- clinical categories at higher risk for adverse reactions;
- criteria for choosing the active substance;
- dosing indications (amount, duration, administration patterns) according to clinical context;
- perceived barriers to appropriate prescription in everyday practice;
- and the extent to which economic considerations influence therapeutic decision-making.

Results

The retrospective analysis of hospital discharge data identified a total of 999,739 pediatric patients (aged 0-17 years) discharged between 2010 and 2016 with diagnoses associated with DRGs potentially related to the use of fever and pain management medications.

Among them, 4,308 patients (0.43%) experienced clinically significant complications during the three-year follow-up period. These cases were identified through the presence of specific ICD-9-CM codes as the primary diagnosis in subsequent hospital admissions.

Table 3 presents a breakdown by DRG, reporting for each area the number of discharges, complication rates, number of affected patients, related hospitalizations, total cost to the healthcare system, and average cost per hospitalization with complications.

These results show that, among pediatric patients discharged with conditions of potential relevance to fever and pain medication use, approximately 0.43% developed complications over the following three years.

TABLE 3 - Distribution of Pediatric Patients (0-17 years) with Complications Occurring Within 3 Years After Discharge, by DRG (2010-2016)

DRG Description	Patients	Complication Rate	Patients with Complications	Related Admissions	Total Cost	Avg. Cost per Case
Other kidney and urinary tract diagnoses	18.216	2,00%	365	460	1.391.079 €	3.811 €
Other digestive system diagnoses	47.875	0,12%	59	63	140.677 €	2.384 €
Appendectomy	95.298	0,07%	63	67	172.715 €	2.742 €
Bronchitis and asthma	166.196	0,12%	192	205	474.117 €	2.469 €
Esophagitis, gastroenteritis, and other digestive conditions	219.988	0,13%	277	305	697.207 €	2.517 €
Kidney and urinary tract infections	44.902	0,44%	196	220	541.042 €	2.760 €
Respiratory tract infections and inflammations	7.723	0,56%	43	48	232.478 €	5.406 €
Otitis media and upper respiratory infections	116.192	0,46%	538	583	1.120.836 €	2.083 €
Simple pneumonia and pleuritis	119.870	0,14%	162	185	537.208 €	3.316 €
Syncope and collapse	21.783	0,07%	15	15	33.872 €	2.258 €
Tonsillectomy and/or adenoidectomy	141.696	1,69%	2.398	2.548	6.303.768 €	2.629 €
Total (Italy 2010-2016)	999.739	0,43%	4.308	4.699	11.644.997 €	2.703 €

The distribution by DRG highlights specific clinical areas where complications were more frequent and where the associated resource use was more substantial. While the data do not allow for a direct attribution of these complications to a specific drug, they underline the importance of prudent prescribing and suggest that inappropriate treatment strategies may carry not only clinical consequences but also a measurable economic burden.

The highest complication rates were observed among children discharged with diagnoses related to non-infectious urinary tract conditions (2.00%) and ENT procedures such as tonsillectomy or adenoidectomy (1.69%), followed by cases involving lower respiratory tract infections and inflammations (0.56%) and otitis media or upper respiratory infections (0.46%). These findings suggest increased clinical vulnerability in certain diagnostic categories, which may be influenced—among other contributing factors—by suboptimal management of fever and inflammation.

The analysis of hospitalization costs associated with these complications further reveals substantial variability, both in total spending and in the average cost per case. The highest economic burden was recorded in DRGs related to ENT surgery (over €6.3 million), upper respiratory tract infections (over €1.1 million), and renal and urinary complications. Equally relevant is the mean cost per complication-related admission, which exceeded €5,400 for cases of severe respiratory infection, compared to typical values ranging from €2,000 to €3,800 in other diagnostic groups.

These results offer a preliminary quantitative picture of the potential clinical and economic impact associated with suboptimal fever management in pediatric care. They show how certain conditions—particularly in younger children—may evolve unfavorably, possibly because of therapeutic decisions that are not fully aligned with best practices. While this analysis does not infer a direct causal link between inappropriate medication use and observed outcomes, the hypothesis of such an association was central to the study design and will be further explored in the following case study.

Lastly, the cost analysis by patient age highlights significant disparities in the financial burden of complication management across pediatric age groups, as shown in Figure 1.

The most striking finding relates to the youngest age groups: children under the age of three—particularly infants—account for the largest share of total complication-related healthcare costs. This pattern points to not only a greater clinical vulnerability among the youngest patients in developing complications, but also to the higher complexity and cost intensity associated with their care.

By contrast, costs tend to decline progressively in older pediatric age groups and stabilize during school-age and adolescence. Figure 2 illustrates the annual trend in pediatric hospitalizations by therapeutic indication, alongside the evolution of mean costs associated with complications over the 2010-2016 observation period.

The temporal analysis reveals a relatively stable number of pediatric hospitalizations over the seven-year period, with minor annual fluctuations reflecting the epidemiological patterns of specific conditions (e.g., seasonal infections, epidemic waves).

What stands out more clearly, however, is the growing variability in average complication-related costs, with marked increases in certain years—particularly those coinciding with peaks in hospitalizations for respiratory infectious diseases.

This trend is consistent with the hypothesis that, beyond the absolute number of admissions, variation in complication severity and case-mix complexity influences healthcare expenditure. The observed increases in average costs may reflect more severe clinical presentations or differences in early-stage management; however, these possibilities cannot be ascertained from administrative data alone. These

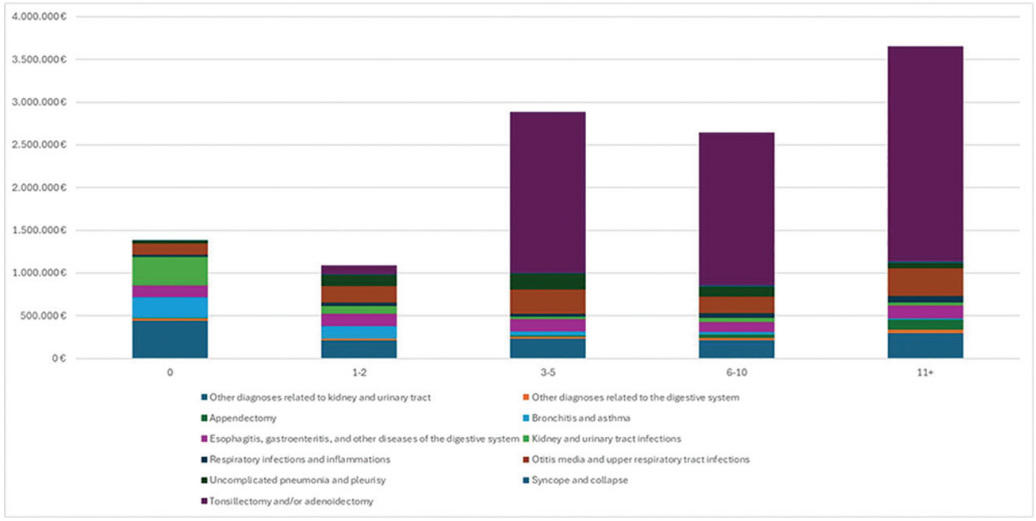

FIGURA 1 - Total Cost Distribution for Complication Management by Age Group.

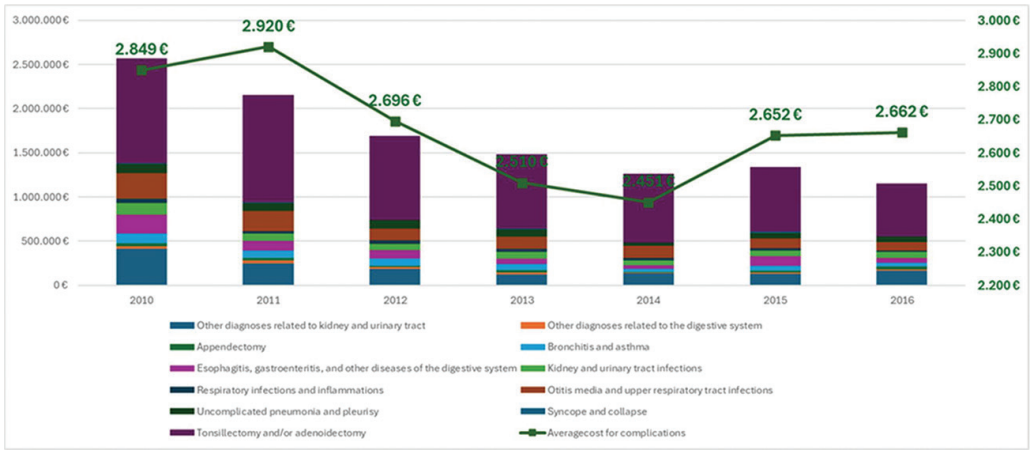

FIGURA 2 - Trends in Pediatric Hospital Admissions by Therapeutic Indication and Average Complication Costs (2010-2016).

descriptive patterns are consistent with broader considerations about treatment appropriateness across levels of care.

The qualitative survey of experts further confirmed several shared areas of clinical concern. The panel expressed a clear preference for paracetamol at 15 mg/kg up to four times per day in the following clinical situations:

- Varicella
- Pneumonia
- Acute respiratory infections
- Gastrointestinal disturbances with risk of dehydration
- Renal disorders with potential for acute kidney injury
- Kawasaki disease under acetylsalicylic acid treatment
- Post-operative management in ENT procedures (e.g., tonsillectomy) and general surgery (e.g., appendectomy).

These recommendations reflect an effort to minimize the risk of complications through more selective use of fever and pain relief medications, which are in line with current evidence and guideline-based practice.

Among the key barriers to appropriate prescribing, the panel identified:

- parental pressure for rapid symptom resolution,
- frequent use of self-medication at home,
- and the persistence of established clinical habits among pediatricians that may not always align with the most recent recommendations.

In response to these issues, the experts emphasized the need to reinforce the prescribing role of pediatricians, promote educational interventions for families, and support the wider adoption of shared best practices across all levels of care.

Discussion

This section provides a descriptive interpretation of administrative data; findings are associative and not intended for causal inference.

To support interpretation of the study findings, a scenario analysis was conducted to estimate the potential clinical and economic impact of prescribing appropriateness in children with community-acquired pneumonia. The analysis draws on data from the observational study by François et al. (23),

conducted in France between 1995 and 2003 on 767 children (aged 28 days to 15 years) hospitalized with a diagnosis of pneumonia. Among these, 90 patients (11.7%) developed suppurative complications such as pleural empyema and/or lung abscess.

In the source study, pre-hospital ibuprofen use was associated with suppurative complications in children with community-acquired pneumonia (adjusted OR 2.57). The authors reported a population-attributable fraction of 22%. In our analysis, this figure is applied illustratively to gauge the order of magnitude of potentially preventable events and costs, not to infer individual-level causality.

In this study, that proportion was applied to national administrative data. Specifically, we considered the 119,870 pediatric hospitalizations with a diagnosis of simple pneumonia and pleuritis (DRG 091) recorded in the Italian SDO discharge database from 2010 to 2016.

By applying the complication rate observed in the French study (11.7%), we estimate approximately 14,025 cases of suppurative complications in Italy during the period considered. Of these, around 3,085 cases (22%) could theoretically be avoidable through more selective and cautious use of NSAIDs in the pre-hospital phase.

Given an average cost per complication of €3,316, the potentially avoidable financial burden for the National Health Service would exceed €10.2 million over the same period.

External validity is limited by temporal and organizational changes since 1995–2003 (e.g., epidemiology, care pathways, stewardship practices); therefore, these projections should be viewed as indicative rather than precise forecasts.

Although the administrative data do not permit attribution of individual complications to pre-hospital ibuprofen exposure, the estimates derived here should be interpreted as illustrative, order-of-magnitude projections of the potential impact of improved prescribing.

Avoiding NSAID use in pediatric patients with signs of severe respiratory infection is one of the key evidence-based indications, relevant both from a safety and cost-containment perspective.

The findings from the retrospective analysis highlight the significant clinical and economic burden associated with the management of complications in pediatric care, especially in situations where fever-reducing medications may not have been used optimally. In some diagnostic categories—such as respiratory infections, post-operative ENT complications, and renal conditions—the percentage of patients with complications was higher than average, pointing to the importance of appropriate therapeutic choices early in the disease course.

Age-specific analysis revealed a concentration of costs among children under the age of three, in line with existing literature recommending greater caution with ibuprofen in this age group (4,12,19). In these patients, paracetamol is often preferred, both for its safety profile and for the lower incidence of renal or gastrointestinal adverse effects (19–27).

The integration of qualitative data from the expert panel reinforced these findings, clearly identifying clinical contexts where paracetamol is preferred, and highlighting key barriers to prescribing appropriateness, such as parental pressure, home self-medication, and inconsistencies in recommendations across care settings.

Overall, the results suggest that more thoughtful and context-specific prescribing, led by pediatricians and supported by targeted education for families, may represent an effective strategy to prevent complications and optimize healthcare resource use.

Limitations and Future Perspectives

This study has several limitations that should be taken into account when interpreting the results. First, the retrospective analysis of administrative data does not allow for a direct causal link to be established between inappropriate use of fever-reducing medications and the observed complications, but rather permits the identification of associations that are consistent with what has been reported in the literature. External validity is limited by temporal and organizational changes since 1995-2003 (e.g., epidemiology, care pathways, stewardship practices). Accordingly, these projections are intended as indicative rather than precise forecasts.

Moreover, the identification of complications was based on ICD-9-CM and DRG coding systems, which, although standardized, may not capture all relevant clinical nuances.

Regarding the qualitative survey, the limited number of experts involved and the absence of a formal consensus process represent an additional constraint. However, this limitation is partly mitigated by the strong alignment between expert opinions and current evidence.

Finally, the scenario analysis—though based on solid data—relies on a simplified model that assumes a uniform distribution of risk and exposure across the pediatric population, without accounting for local organizational or clinical differences.

Conclusions

In a nationwide administrative dataset, we describe associations between pediatric hospitalizations for selected complications and contexts in which antipyretics are commonly used. While not designed for causal inference, the findings are consistent with the need for careful, context-specific prescribing—particularly for ibuprofen in vulnerable children—and for strengthening caregiver education on correct dosing of paracetamol and ibuprofen. At the system level, periodic updates to pediatric guidance, communication initiatives on dosing accuracy, and audit-and-feedback programs may help improve appropriateness and reduce avoidable costs.

Disclosures

Conflict of interest: The authors declare they have no conflict of interest related to the article.

Financial support: This study was funded by Angelini Pharma S.p.a.

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