

ORIGINAL RESEARCH

Development of a Five-Checkpoint Framework for Paediatric Adverse Drug Reactions: A Retrospective Pharmacovigilance Study

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ABSTRACT

Background: Paediatric pharmacovigilance studies usually describe which drugs caused which reactions; few use adverse drug reaction (ADR) reports to identify practical opportunities to make medication use safer. A simple five-checkpoint framework was developed for this purpose and applied to paediatric ADR reports. **Methods:** All ADR reports concerning patients younger than 18 years received by an ADR Monitoring Centre (AMC) in Kerala, India, from 2021 to June 2026 were reviewed retrospectively using VigiFlow entries and the original reporting forms. Each report was examined at five checkpoints in the medication pathway: indication, dose, add-on drugs, the pre-dose step and the response to the reaction. Potential preventability was assessed with the Schumock–Thornton criteria. **Results:** Of 168 unique ADR reports received by the AMC between 2020 and 2026, 16 (9.5%) involved patients younger than 18 years (11 boys; age 4–14 years). Antibiotics were suspected in 13. In every case the reaction was recognised, the suspected drug was stopped and the event was reported, and all children had recovered or were recovering. At least one opportunity for safer care was identified in 11 reports (68.8%): antibiotic use for upper respiratory infection or fever without documented bacterial infection (4 of 14 assessable reports), doses outside the usual weight-based range (2 of 7), routine co-prescription of pantoprazole (5 of 16), intradermal test doses (4 of 16), and an immediate systemic reaction managed without recorded adrenaline (1 of 2). Weight was not recorded in half of the ADR reports. Five reactions (31.3%) were judged potentially preventable. **Conclusions:** A five-checkpoint review turned individual ADR reports into concrete opportunities for system-level improvement, including decision support for antibiotic selection, weight-based dosing aids, revised order sets, replacement of routine test doses, and adrenaline-first anaphylaxis protocols. The framework may help AMCs give structured, constructive feedback, but it requires evaluation in larger, multicentre datasets.

Keywords: Adverse drug reaction; child; medication safety; quality improvement; pharmacovigilance; antimicrobial stewardship; India

Key points: What is already known: Antibiotics are the most common cause of adverse drug reactions in children, and some paediatric ADRs are preventable through system-level measures. **What this study adds:** A simple five-checkpoint review of paediatric ADR reports identified specific, practical opportunities for safer medication use in two of every three reports, alongside consistent good practice in recognising, managing and reporting reactions. **How this might change practice:** ADR Monitoring Centres can use the same five questions to give constructive, non-judgemental feedback to clinical teams and to target stewardship and medication-safety initiatives.

INTRODUCTION

Adverse drug reactions (ADRs) affect about 1 in 10 hospitalised children and account for around 2% of paediatric hospital admissions [1]. Antibiotics are the drugs most often implicated, and the skin is the organ most commonly affected [2,3]. Children are particularly vulnerable because doses must be calculated by weight, suitable formulations are often unavailable, and much paediatric prescribing is off-label.

Most pharmacovigilance studies describe which drugs caused which reactions. This shows what happened, but not why, or where the reaction might have been prevented. The World Health Organization's third Global Patient Safety Challenge, Medication Without Harm, calls for medication-related harm to be understood as the result of a sequence of decisions and

system weaknesses rather than as isolated events [4]. Reason's "Swiss cheese" model makes the same point: harm usually reaches the patient not through one person's error but when weaknesses in several layers of a system line up, and safety improves most when those layers are strengthened rather than when individuals are blamed [5].

Spontaneous reports received by ADR Monitoring Centres (AMCs) under the Pharmacovigilance Programme of India [6] often contain enough clinical detail, particularly in the original handwritten forms, to reconstruct these decisions. A simple five-checkpoint framework was therefore designed as a learning tool, not an audit of individual performance, and applied to the paediatric ADR reports received by one AMC to identify where medication use could be made safer.

MATERIALS AND METHODS

Setting and data sources

All ADR reports received by the AMC of a tertiary care teaching hospital in Thiruvananthapuram, Kerala, India, from Jan 2021 to June 2026 were reviewed. For each report, both the VigiFlow entry and the original suspected-ADR reporting form were examined. Reports concerning patients younger than 18 years were included, and duplicate reports were excluded.

Description of reactions

Age, sex, weight, diagnosis, suspected and concomitant drugs, dose, route, clinical features, seriousness, management, outcome and the WHO–Uppsala Monitoring Centre (WHO-UMC) causality category assigned by the AMC [7] were recorded. Anaphylaxis was assessed against the World Allergy Organization 2020 criteria [8].

Development of the framework

The framework was developed by mapping the main decision points in the paediatric medication pathway onto the factors used in established preventability criteria [9] and in the WHO Medication Without Harm framework [4]. It was then applied as a pilot to all eligible paediatric reports.

Five-checkpoint analysis

Each report was examined at five successive points in the pathway from prescription to reaction (Figure 1). At each checkpoint, the reviewer recorded whether the report showed an opportunity for safer care, showed none, or could not be assessed because the necessary information was missing or the checkpoint did not apply. Because reports capture only part of the clinical picture, an opportunity identified in this way indicates a point for review, not a judgement on the individual decision.

The checkpoints were defined as follows. **Checkpoint 1 (indication):** an antibiotic prescribed for upper respiratory infection or undifferentiated fever when the report did not document evidence of bacterial infection. **Checkpoint 2 (dose):** where weight was recorded, a dose per kilogram outside the usual range in a standard paediatric formulary [10]. **Checkpoint 3 (add-on drugs):** co-prescription of a drug without a clear indication, which in practice was a proton pump inhibitor given routinely as "gastric cover". **Checkpoint 4 (pre-dose step):** an intradermal test dose given before the full dose. **Checkpoint 5 (response):** for immediate systemic reactions requiring emergency treatment, whether adrenaline was recorded as given.

Potential preventability was assessed using the Schumock–Thornton criteria [9]. All reports were assessed by the author using these predefined decision rules.

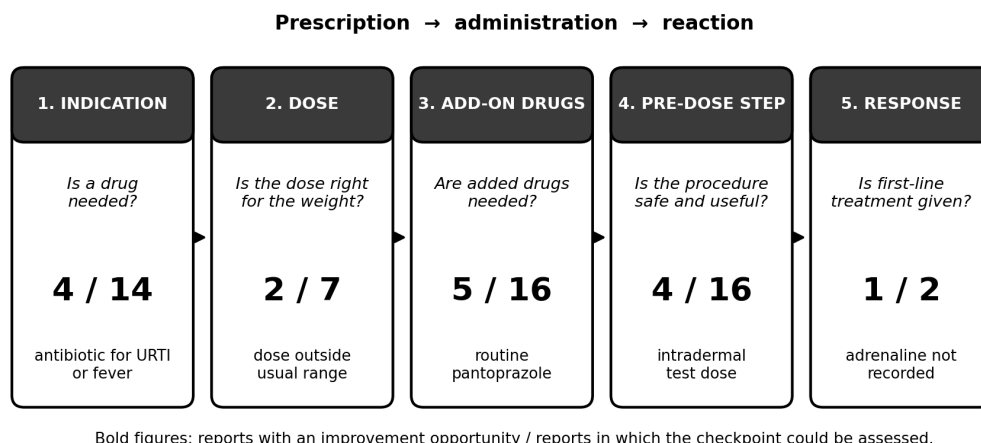


Figure 1. The five-checkpoint framework, showing at each checkpoint the number of reports with an opportunity for safer care / the number of reports in which the checkpoint could be assessed. URTI, upper respiratory tract infection.

RESULTS

The reactions

Sixteen paediatric reports were analysed (Table 1). Eleven patients were boys; ages ranged from 4 to 14 years, and no infants were reported. Antibiotics were suspected in 13 reports (81.3%), most often amoxicillin with or without clavulanate ($n = 7$) and cephalosporins ($n = 4$); the remaining suspected drugs were tramadol, an iodinated contrast medium and docusate ear drops. Twelve reactions were cutaneous or mucocutaneous. The others were anaphylaxis after intravenous amoxicillin–clavulanate, a systemic reaction to contrast medium, cytopenias with a positive direct Coombs test during ceftriaxone and piperacillin–tazobactam therapy, and abdominal pain after cefixime. Four reactions were serious and none was fatal. Causality was assessed as probable in eight reports and possible in eight.

Table 1. Characteristics of the 16 paediatric ADR reports

Characteristic	n (%)
Reports	16
Boys / girls	11 (68.8) / 5 (31.3)
Age 1–5 / 6–11 / 12–17 years / not recorded	5 / 6 / 4 / 1
Weight recorded	8 (50.0)
Suspected drug: amoxicillin ± clavulanate / cephalosporin	7 (43.8) / 4 (25.0)
Suspected drug: azithromycin, clindamycin, tramadol, contrast medium, ear drops	1 each
Route: oral / intravenous / intradermal / topical	7 / 7 / 1 / 1
Reaction: cutaneous or mucocutaneous	12 (75.0)
Reaction: systemic / haematological / gastrointestinal	2 / 1 / 1
Serious	4 (25.0)
WHO-UMC causality: probable / possible	8 / 8
Improvement opportunity at ≥ 1 checkpoint / at 2 checkpoints	11 (68.8) / 5 (31.3)
Potentially preventable (Schumock–Thornton)	5 (31.3)
Reaction recognised, drug stopped and reported	16 (100)

ADR, adverse drug reaction; WHO-UMC, World Health Organization–Uppsala Monitoring Centre.

Good practice observed

In all 16 cases, the reaction was recognised, the suspected drug was stopped promptly, and the event was reported to the AMC, reflecting an active reporting culture. At the time of reporting, all children had recovered or were recovering. Where these checkpoints could be assessed, the antibiotic was clearly indicated in 10 of 14 reports and correctly dosed in 5 of 7. The child who developed urticaria and angioedema after amoxicillin received correctly dosed intramuscular adrenaline.

Opportunities for safer care at each checkpoint

At least one opportunity for safer care was identified in 11 of the 16 reports (68.8%), and two opportunities in 5 reports (Figure 1; Table 2). At the indication checkpoint, 4 of 14 assessable reports involved an antibiotic given for upper respiratory infection or fever without documented evidence of bacterial infection. At the dose checkpoint, weight was recorded in eight reports; of the seven in which the dose per kilogram could be calculated, two were outside the usual range, one lower (oral amoxicillin, about 8 mg/kg/day) and one higher (intravenous amoxicillin–clavulanate, about 127 mg/kg/day). At the add-on checkpoint, five children had received pantoprazole, usually recorded as prophylaxis against gastritis. At the pre-dose checkpoint, four children had received an intradermal test dose in line with established local practice: one reacted to the test dose itself, and three reacted to the full dose after a negative test. At the response checkpoint, adrenaline was not recorded for one of the two children who needed emergency treatment for an immediate systemic reaction.

Five reactions (31.3%) were judged potentially preventable by the Schumock–Thornton criteria: four in which the indication or dose could have been reconsidered, and one reaction to a test dose.

Table 2. Opportunities for safer care identified at each checkpoint

No.	Age (y)/ sex	Suspected drug	Reaction	C1	C2	C3	C4	C5	PP
1	6/F	Amoxicillin syrup	Urticaria, angioedema	Yes	Yes	–	–	–	Yes
2	4/M	Ceftriaxone → piperacillin–tazobactam	Erythematous rash	–	–	–	Yes	NA	No
3	5/M	Docusate ear drops	Contact reaction, pinna	–	NA	–	–	NA	No
4	10/M	Iodinated contrast	Cough, tachypnoea, itching	–	NA	–	–	Uncertain	No
5	14/F	Tramadol (test dose)	Test-site induration	–	NA	Yes	Yes	NA	Yes
6	4/M	Amoxicillin–clavulanate IV	Anaphylaxis (hypotension)	–	NA	Yes	–	Yes	No
7	8/F	Azithromycin	Urticaria	Yes	–	–	–	NA	Yes
8	14/M	Clindamycin	Recurrent rash	–	NA	Yes	–	NA	No
9	4/M	Ceftriaxone → piperacillin–tazobactam	Cytopenias, DCT positive	–	–	–	–	NA	No
10	5/M	Ceftriaxone IV	Injection-site induration	–	–	Yes	Yes	NA	No
11	NR/F	Amoxicillin–clavulanate syrup	Rash, itching	NA	NA	–	–	NA	No
12	6/M	Amoxicillin–clavulanate IV	Erythematous rash	Yes	Yes	–	–	NA	Yes
13	6/F	Cefixime syrup	Abdominal pain	Yes	NA	–	–	NA	Yes
14	12/M	Amoxicillin–clavulanate	Maculopapular rash	–	NA	Yes	–	NA	No
15	6/M	Amoxicillin–clavulanate syrup	Itching, rash, induration	NA	NA	–	–	NA	No
16	12/M	Amoxicillin–clavulanate IV	Itching	–	–	–	Yes	NA	No
Total				4/14	2/7	5/16	4/16	1/2	5/16

C1, indication; C2, dose; C3, add-on drugs; C4, pre-dose step; C5, response; PP, potentially preventable. Yes, improvement opportunity identified; –, none identified; NA, not assessable (information missing or checkpoint not applicable); Uncertain, adequacy of management could not be determined from the report (contrast reaction with respiratory features treated with an antihistamine and hydrocortisone). Totals are reports with an opportunity / reports in which the checkpoint could be assessed. Potential preventability was assessed with the Schumock–Thornton criteria. DCT, direct Coombs test; F, female; IV, intravenous; M, male; NR, not recorded.

Learning cases

Learning case A: a reaction to a low dose (checkpoints 1 and 2). A 6-year-old girl weighing 18.9 kg with fever and an upper respiratory infection was prescribed amoxicillin syrup 75 mg twice daily at a primary health centre, about 8 mg/kg/day compared with a usual range of 40–90 mg/kg/day. Within minutes of the first dose, she developed urticaria and angioedema. She was treated promptly in the paediatric intensive care unit, including with correctly dosed intramuscular adrenaline, and recovered within 30 minutes. The case shows that even a low dose can provoke a serious immediate reaction, and that weight-based dosing aids and clear guidance on antibiotic use in respiratory infections could support prescribers in busy primary care settings.

Learning case B: when a precaution becomes the reaction (checkpoint 4). A 14-year-old girl with acute pancreatitis was given an intradermal test dose of tramadol before an infusion, as is customary in many Indian hospitals. Induration and redness developed at the test site within 10 minutes. The test dose, intended as a safety precaution, was itself the only adverse event, illustrating why test-dose protocols merit review.

Learning case C: the place of adrenaline (checkpoint 5). A 4-year-old boy with asthma developed generalised urticaria and hypotension 25 minutes after intravenous amoxicillin–clavulanate. The reaction was recognised promptly, the drug was stopped and hydrocortisone was given, and he recovered within an hour. Adrenaline was not recorded. Because the reaction met the criteria for anaphylaxis, current guidance would place intramuscular adrenaline (0.01 mg/kg) first [8], a point that weight-based adrenaline charts and team drills can reinforce.

Learning case D: a reaction beyond the skin. A 4-year-old boy with pneumococcal pneumonia developed anaemia, leucopenia and severe thrombocytopenia with a positive direct Coombs test during treatment with ceftriaxone followed by piperacillin–tazobactam. Sepsis was an important confounder, but drug-induced immune haemolysis, a recognised reaction to ceftriaxone in children [11], had to be considered. No opportunity for improvement was identified. The case shows that not every ADR is preventable and that vigilance for less common reactions is needed.

DISCUSSION

Applying a simple five-checkpoint framework to paediatric ADR reports identified specific opportunities for safer medication use in two of every three reports, while also showing consistent good practice in recognising, treating and reporting reactions. The value of the approach is that each opportunity points to a practical, system-level improvement rather than to individual fault (Table 3).

The prescribing decisions examined here were made in real-world conditions: busy outpatient clinics, parents expecting antibiotics for a febrile child, weighing scales and paediatric formulations that are not always available, order sets that include acid suppression by default, and long-standing institutional customs such as test dosing. Reports also capture only part of the clinical picture, so a decision that appears unsupported on the form may have been well founded. The findings should therefore be read as reflecting systems and supports rather than individual clinicians.

Indication. Antibiotics were prescribed to four children with respiratory infection or fever without documented evidence of bacterial infection. Antibiotics are frequently prescribed for respiratory infections in Indian outpatient practice [12], often without a definitive diagnosis and in response to parental expectations. Clinical decision support and stewardship programmes that help prescribers safely withhold or delay antibiotics are therefore valuable. A related point is that many rashes that appear during a viral illness treated with amoxicillin are not allergic; in a prospective rechallenge study, only about 7% of such children reacted again [13]. Children labelled as penicillin-allergic on the basis of such rashes may lose access to first-line antibiotics for life, so non-severe reactions should be evaluated and, where appropriate, the allergy label removed [14].

Dose. Weight, the basis of all paediatric dosing, was not documented in half of the reports, and where it was, two of seven doses fell outside the usual range. Paediatric dosing is genuinely demanding, particularly with liquid formulations of different strengths. Systems that record weight automatically, printed weight-band dosing charts and pharmacist review make accurate dosing easier for everyone.

Add-on drugs. Five children received pantoprazole, usually as routine “gastric cover”, a widespread habit that is often built into standard orders. Proton pump inhibitors have their own adverse effects in children [15], and each additional drug adds another suspect when a reaction occurs. Revising order sets so that acid suppression is prescribed only for a stated indication is a simple system change.

Pre-dose step. Test dosing is a well-intentioned and widely taught practice, but bedside intradermal test doses have not been validated for predicting immediate reactions [14,16]. In this series, one child reacted to the test dose itself and three reacted after a negative test. Replacing routine test doses with a careful allergy history and observation after the first dose would spare children an extra injection, but this change requires institutional policy support rather than individual decisions.

Response. Intramuscular adrenaline is the first-line treatment for anaphylaxis at any age [8]. One child received correctly dosed adrenaline; the other recovered after hydrocortisone, and adrenaline was not recorded. Weight-based adrenaline charts kept with emergency drugs, together with regular team drills, help all staff act quickly and confidently.

The framework has uses beyond this analysis. AMCs could apply the same five questions to each paediatric report and share the findings with clinical teams in a supportive, educational way, turning pharmacovigilance from a counting exercise into a shared learning tool. Such feedback works best when it acknowledges good practice as well as opportunities for improvement. The questions are simple enough for residents and nurses to use, and the categories map directly onto existing programmes in antimicrobial stewardship, medication safety and emergency care.

Table 3. From learning to action: system changes suggested by the five-checkpoint review

Checkpoint	Opportunity identified	Supportive system change	Responsibility
1. Indication	Antibiotics for upper respiratory infection or fever	Local guidance and decision support for antibiotic use in acute respiratory infection; information leaflets for parents	Prescribers; antimicrobial stewardship team
2. Dose	Doses outside the usual weight-based range; weight not recorded	Routine recording of weight; weight-band dosing charts; pharmacist review	Prescribers; pharmacy
3. Add-on drugs	Routine pantoprazole as “gastric cover”	Remove routine acid suppression from standard order sets; require a stated indication	Clinical departments; drug and therapeutics committee
4. Pre-dose step	Intradermal test doses	Institutional policy replacing routine test doses with an allergy history and 30-minute observation after the first dose	Nursing; drug and therapeutics committee
5. Response	Adrenaline not recorded in anaphylaxis	Weight-based intramuscular adrenaline chart kept with emergency drugs; regular drills	Paediatric and emergency teams
Reporting	Weight and indication missing from ADR reports	Make weight and indication required fields when ADRs are reported	ADR Monitoring Centre

ADR, adverse drug reaction.

Strengths and limitations

The main strengths of this study are the use of original reporting forms, which allowed prescribing decisions to be reconstructed in a way that database records alone would not permit, and a simple, transparent framework. The limitations are substantial. The series is small and from a single centre, and the reports screened may not include every paediatric report received. Because spontaneous reporting systems under-report mild and outpatient reactions, the findings cannot be used to estimate incidence. Missing information on weight and indication meant that some checkpoints could not be assessed, so some opportunities may have been missed. The checkpoint and preventability assessments were made retrospectively from incomplete records and involved clinical judgement, although explicit criteria were applied, and the clinicians’ full reasoning could not be known. All assessments were made by a single reviewer, so inter-rater reliability could not be assessed. Finally, the framework was developed and piloted in one centre, and its reliability and usefulness need to be validated in larger, multicentre datasets.

CONCLUSIONS

A simple five-checkpoint review of paediatric ADR reports identified practical opportunities for safer medication use in most reports, alongside consistent good practice in recognising, treating and reporting reactions. Asking five questions of every report (Is a drug needed? Is the dose right? Are add-on drugs needed? Is the pre-dose step safe and useful? Is first-line treatment given?) can help ADR Monitoring Centres and clinical teams work together to make medicines safer for children.

DECLARATIONS

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