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ORIGINAL ARTICLE

# Incidence and nature of adverse drug events in paediatric intensive care units: A prospective multicentre study

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**Aims:** The aim of this study was to assess the incidence, nature, preventability and severity of adverse drug events (ADEs) across three paediatric intensive care units (PICUs) in England.

**Methods:** A prospective observational cohort study was conducted across three PICUs over a three-month period during 2019. Included patients were aged ≤18 years and stayed in PICU for a minimum of 24 hours. Identification of suspected ADEs was performed by trained PICU pharmacists. A multidisciplinary expert panel assessed causality, preventability and severity of events.

**Results:** A total of 302 patients were included and 62 ADEs were confirmed (definite/probable causality). One in six patients experienced one or more ADEs. The estimated incidence of ADEs were 20.5 per 100 patients (95% CI 15.3–27.5) and 16.7 per 1000 patient-days (95% CI 9.3–29.9). The majority of ADEs were judged preventable by the expert panel (36/62, 58.1%). ADEs were commonly involved with medicines prescribing (29/62, 46.8%) and caused temporary patient harm (42/62, 67.7%). Medications for the central nervous system (14/62, 22.6%), infections (13/62, 20.9%) and cardiovascular system (12/62, 19.4%) were commonly implicated with ADEs. Multivariable analysis revealed that patients who stayed in PICU for ≥7 days (OR 6.29, 95% CI 2.42–16.32) were more likely to experience an ADE compared to patients with a stay of 1–6 days.

**Conclusion:** ADEs are common in English PICUs and most of them may be preventable. There is a strong association between ADE occurrence and duration of PICU stay, which represents a target for remedial interventions. Exploring contributory factors of preventable ADEs is now necessary to inform preventive policies.

KEYWORDS
adverse drug events, medication safety, paediatric critical care, paediatric intensive care, patient safety

In this study no interventions were performed and no substances were administered to human subjects/patients.

## 1 | INTRODUCTION

The use of medication is a principal component of patient care and among the most common causes of adverse events in hospital settings.[1] Some adverse drug events (ADEs) are preventable, such as complications resulting from medication errors, while some are non-preventable and are called adverse drug reactions (ADRs).[2] ADEs vary in severity ranging from a non-significant drug rash to permanent disability or death.[3,4] Within the National Health Service (NHS) in England, definitely preventable ADEs contribute to 1708 hospital admissions and cause 712 hospitalised patient deaths per year. These ADEs were found to cost the health care system around £98.5 million annually.[5]

Harm associated with using medications may be common in paediatric inpatients. In the United States, four studies published between 2001 and 2008 examined the incidence of ADEs in hospitalised children (three of them at multiple hospital sites), reporting rates ranging from 2.3 to 11.2 per 100 patients.[4,6–8] ADEs in children may be commonly preventable. For example, in a systematic review that was conducted in 2012 to examine ADRs (preventable and non-preventable) in paediatric patients across all health care settings, 7% to 98% of all ADRs reported in 14 studies were classified as preventable.[9]

In our recent systematic review,[10] we found that preventable ADEs might be common in critically ill children admitted to neonatal and paediatric intensive care units (NICU and PICU) based on four studies conducted across three different countries. However, we observed limited available data regarding preventable ADEs in this high-risk patient population, particularly in UK hospitals. This represents a significant knowledge gap and barrier to improvement efforts given also differences in care and medicines management processes.[10]

Studies identifying and reporting drug-related harms in children would help highlight areas of necessary guidance to prescribers to improve medication safety and enhance awareness of the actual occurrence of patient harm due to deficiencies in the process of medication use.[11] In addition, preventable ADEs are the most amenable event to remedial actions and are important targets for improvement.[12] We therefore aimed to determine the incidence, nature, preventability and severity of ADEs occurring in critically ill children at UK hospitals with a particular emphasis on preventable ADEs.

### What is already known about this subject

- The risk of adverse drug events (ADEs) may be greater in paediatric intensive care units (PICUs) than other general hospital wards.
- There is lack of evidence concerning the burden and nature of ADEs in PICUs.

### What this study adds

- One in six PICU patients experienced one or more ADEs.
- The majority of ADEs in PICUs are preventable and likely to occur in patients with increased length of stay.
- Medications for central nervous system and cardiovascular system were commonly involved with ADEs.
- The most serious ADEs were associated with the use of high-risk medicines (e.g., anticoagulants).

## 2 | METHOD

### 2.1 | Study design and setting

The study utilised a prospective cohort design and was carried out on consecutive weekdays over a three-month period (90 days) during 2019 across three NHS children's hospitals in England. The study took place in three PICUs (17 [PICU-C], 18 [PICU-B] and 31 [PICU-A] bedded units) that provide regional acute care specialities for new-born infants and children up to 18 years of age in the North West, West Midlands, South West of England and South Wales.

### 2.2 | Eligible patients

All patients admitted to any participating PICU and who stayed for a minimum of 24 hours (including those already admitted when the study started) during the study period were eligible for inclusion. In order to include similar patient populations in terms of severity and complexity of health condition who were receiving care for critical illnesses, high dependency unit or level 1 PICU patients were excluded as they are normally admitted to PICUs to facilitate close monitoring only.

Each included patient reached the study endpoint only if they were transferred to another inpatient ward/unit/hospital, discharged into the community, died or remained an inpatient on the PICU at the end of the study data collection period.

### 2.3 | Classification of adverse drug events and main outcomes

ADEs were defined as "injuries that result from the use of a drug".[6] ADE is a broad term that encompasses injury that is a result of both medication errors or unavoidable side effects. Harm associated with a medication error was considered preventable. Both preventable and non-preventable ADEs were collected for this study. However, this study is based on the findings of our earlier systematic review,[10] hence an important focus was on ADEs that were preventable.

The primary outcome measure was to determine the frequency of ADEs and preventable ADEs per 100 patients and 1000 patient-days. The secondary outcome measures were assessing identified ADEs' causality, preventability, severity, involved medications and stage of medication use process with ADEs as well as examining risk

factors associated with ADEs and preventable ADEs in PICUs. Risk factors were identified by assessing the association between the occurrence of ADEs and characteristics of patients including age, number of medications on admission, duration of follow-up and PICU site.

### 2.4 | Data collection

Intensive surveillance for all suspected ADEs occurring in PICUs was performed by PICU clinical pharmacists (three pharmacists in PICU-A, one in PICU-B and two in PICU-C) employed by host NHS trusts. Pharmacists each received a face-to-face training session delivered by the research team members (A.A. and A.S.) on the data collection process. Demographic information of eligible patients was collected including age at admission, date of admission to the PICU, history of drug allergies and number of medications on the admission date after the medication reconciliation has been completed.

Suspected ADEs were identified through daily screening of medication charts of all inpatients admitted to the study PICUs, along with identification and investigation for any alerts to the occurrence of ADEs. Medical notes, laboratory reports, patient safety incident reports, attending multidisciplinary unit rounds and conversations with staff/patients/families were also used to identify events daily.

### 2.5 | Assessment of causality, preventability and severity

A multidisciplinary expert panel reviewed each recorded event by the data collectors to assess causality, preventability and severity of identified events. The expert panel included two experienced PICU clinical pharmacists (A.S. and J.G.) and one consultant paediatric intensivist (G.M.). Panel members discussed any disagreement to achieve consensus.

The Liverpool ADR causality assessment tool[13] was used to assess the causal relationship between use of drugs and adverse events. This causality algorithm classifies detected ADEs/ADRs into unlikely, possible, probable and definite. Definite or probable ADE categories underwent preventability assessment. This was performed by the expert panel using the feasible Schumock and Thornton preventability scale.[14]

The expert panel also assessed the level of outcome severity of each ADE using categories E though I of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) classifications index.[15]

### 2.6 | Statistical analysis

The statistical analyses were performed using STATA 15®.[16] Descriptive statistics were calculated for characteristics of the patients. Dependent on their distributional form, we presented either mean and standard deviation or median and interquartile range (IQR), plus the range. It was not known exactly how long some patients (4%) stayed in PICU (e.g., some patients remained in PICUs after the study stopped) and, therefore, we have had to assume that they stayed for 90 days.

The incidence rate was calculated per 100 patients and 1000 patient-days. The estimated crude and adjusted (for follow-up period and PICU site) incident rates of ADEs were calculated per 1000 patient-days and per 100 patients, along with 95% confidence intervals (CI). Medications associated with the occurrence of ADEs and preventable ADEs were described and reported according to the classification used in the British National Formulary for Children.[17]

Associations between independent variables and ADEs detected in this study were investigated using univariate and multivariate logistic regression models.

Additionally, we carried out univariate and multivariate multinomial regression. This is because we actually have three possible classifications (no ADE, preventable ADE, non-preventable ADE), but there is no natural ordering to them. Analyses used patients without ADEs as a base outcome and examined two classifications (no ADE *vs* preventable ADE and no ADE *vs* non-preventable ADE).

Only patients who experienced ADEs that were classified as definite or probable were included in the regression analysis. The findings of the regression analysis were presented as odds ratios. A *P*-value of $<0.05$ was considered significant.

## 3 | RESULTS

### 3.1 | Patient characteristics

A total of 302 patients across the three participating PICUs were included during the study period. The patients' age ranged from two days to 18 years old with a median of 365 days (IQR 60 days–6 years). The median number of medications prescribed for patients on admission was 9 (IQR [7, 12]; range = 1–23). In total 3000 medications had been prescribed to the study sample. The range of follow-up was between 2 and 90 days with a median of 6 days (IQR 3–14). Only 12 of the 302 patients (4%) stayed on the PICU for the entire follow-up period (90 days). As the exact follow-up of these 12 patients was unknown, it may have an effect on the ADE rate calculations. Table 1 summarises the characteristics of the patients, both overall and by participating PICU.

### 3.2 | Rate and nature of adverse drug events

In total, 115 ADEs were detected by the clinical pharmacists during the study's follow-up period. Of these, 53 (46.1%) were deemed unlikely or possible causality and were excluded from further assessment. The remaining 62 (53.9%) ADEs were classified as definite (7/62, 11.3%) or probable causality (55/62, 88.7%). Characteristics of

**TABLE 1** Characteristics of included patients

| Participating PICUs | Number of patients *n* (%) | Age (years) Median (IQR) | Follow-up period (days) Median (IQR) | Number of medications on admission Median (IQR) |
|---|---|---|---|---|
| PICU-A | 81 (26.8%) | 0.5 (0.08–5.06) | 5 (3–10) | 8 (6–11) |
| PICU-B | 100 (33.1%) | 1.01 (0.16–8.61) | 6.5 (3–15) | 10 (8–14) |
| PICU-C | 121 (40.1%) | 1.83 (0.32–7.09) | 6 (3–14) | 9 (7–13) |
| Total | 302 (100%) | 1.01 (0.16–6.1) | 6 (3–14) | 9 (7–12) |

PICUs: paediatric intensive care units.

**TABLE 2** Characteristics of patients without adverse drug events, with unlikely or possible adverse drug events and with definite or probable adverse drug events

| Variable | | Patients without ADEs ($n = 255$) | Patients with unlikely or possible ADEs[a] ($n = 42$) | Patients with definite or probable ADEs[b] ($n = 47$) |
|---|---|---|---|---|
| Age in years. Median (IQR) [range: 2 days–18 years] | | 1.01 (0.16–7.1) | 2.3 (0.31–11.2) | 1.7 (0.31–6.1) |
| Follow-up period in days. Median (IQR) [range: 2–90 days] | | 5 (2–10) | 15 (7–34) | 15 (8–32) |
| Number of medications on admission. Median (IQR) [range: 1–23 drugs] | | 9 (7–12) | 10 (8–15) | 12 (8–15) |
| Involved PICUs (*n*, %) | PICU-A | 63 (24.7%) | 20 (47.6%) | 18 (38.3%) |
| | PICU-B | 87 (34.1%) | 8 (19.04%) | 13 (27.6%) |
| | PICU-C | 105 (41.2%) | 14 (33.3%) | 16 (34.04%) |

ADEs: adverse drug events, IQR: interquartile range, PICUs: paediatric intensive care units.
[a]ADEs with unlikely or possible causality as classified by the study's expert panel were excluded from further assessment.
[b]ADEs with definite or probable causality as classified by the study's expert panel were included in the study analysis.

**TABLE 3** Crude and adjusted rates of adverse drug events per 100 patients and 1000 patient-days

| Category | Rate of ADE per 100 patients (95% CI)[a] | | Rate of ADE per 1000 patient-days (95% CI)[a] | |
|---|---|---|---|---|
| | Crude rate | Adjusted rate[b] | Crude rate | Adjusted rate[b] |
| All ADEs | 20.5[d] (95% CI 16.1–25.5) | 20.5 (95% CI 15.3–27.5) | 15.6[d] (95% CI 11.9–20.1) | 16.7 (95% CI 9.3–29.9) |
| Preventable ADEs | 11.9 (95% CI 8.4–6.1) | 11.7 (95% CI 6.7–20.1) | 9.08 (95% CI 6.3–12.5) | 9.43 (95% CI 4.02–22.1) |

ADEs: adverse drug events, CI: confidence intervals.
[a]Number of patients in every 100 patients will have an ADE during the course of their observation.
[b]New ADEs per 1000 patients per day.
[d]The 95% CIs give the degree of uncertainty in these calculations (e.g., between 9.3 and 29.9 new ADEs per 1000 patients per day).
[c]Adjusted rate for follow-up period and paediatric intensive care unit site.

patients experiencing no ADEs, unlikely or possible causality ADEs and definite or probable causality ADEs are presented in Table 2. One in six patients (47/302, 15.6%) experienced at least one confirmed ADE (definite and probable causality) during PICU stay. Eleven patients (3.6%) were affected by more than one ADE. Given that these multiple ADEs were not common and not related to each other (e.g., caused different patient harm by different medications), we treated them as independent events.

The estimated crude and adjusted ADE rates (for duration of follow-up and PICU site) per 100 patients and 1000 patient-days are presented in Table 3. As shown in Table 4, the medicines prescribing stage was most commonly associated with identified ADEs (29/62, 46.8%) and the majority of ADEs (42/62, 67.7%) caused temporary patient harm (the lowest level of severity).

The most commonly involved drug classes associated with ADEs were medicines for the central nervous system (14/62, 22.6%), infections (13/62, 20.9%) and the cardiovascular system (12/62, 19.4%). ADEs that caused severe patient harm (permanent harm and near-death events) were associated with using anti-infectives and cardiovascular agents, with some considered as high-risk medicines (e.g., adrenergic antagonists and aminoglycosides) as shown in Table 5 and Table S1 in the Supporting Information.

**TABLE 4** Stage of medication use process and severity of harm associated with adverse drug events

| All ADEs | Stage of medication use process, *n* (%) Prescribing 29 (46.8%) | Administration 15 (24.2%) | Monitoring 18 (29.03%) | Total, *n* (%) 62 (100%) |
|---|---|---|---|---|
| Severity (NCC MERP index) *n* (%) | | | | |
| E (temporary patient harm) | 20 (47.6%) | 8 (19.05%) | 14 (33.3%) | 42 (67.7%) |
| F (prolonged hospitalisation and temporary harm) | 8 (61.5%) | 3 (23.08%) | 2 (15.4%) | 13 (20.9%) |
| G (permanent harm) | 0 (0.0%) | 3 (75%) | 1 (25%) | 4 (6.4%) |
| H (near-death) | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) | 3 (4.8%) |
| **Preventable ADEs** | **Stage of medication use process, *n*. (%) Prescribing 17 (47.2%)** | **Administration 13 (36.1%)** | **Monitoring 6 (10.3%)** | **Total, *n* (%) 36 (58.1%)** |
| Severity (NCC MERP index) *n* (%) | | | | |
| E (temporary patient harm) | 11 (52.4%) | 7 (33.3%) | 3 (14.3%) | 21 (58.3%) |
| F (prolonged hospitalisation and temporary harm) | 5 (50%) | 3 (30%) | 2 (20%) | 10 (27.8%) |
| G (permanent harm) | 0 (0.0%) | 3 (75%) | 1 (25%) | 4 (11.1%) |
| H (near-death) | 1 (100%) | 0 (0.0%) | 0 (0.0%) | 1 (2.7%) |

ADEs: adverse drug events.
NCC MERP: National Co-ordinating Council for Medication Error Reporting and Prevention.
E: Harm that required intervention and resulted in temporary patient harm.
F: Harm that required initial or prolonged hospitalisation and resulted in temporary patient harm.
G: Harm that resulted in permanent patient harm.
H: Harm that resulted in near-death event and required intervention to sustain life.

**TABLE 5** Commonly involved drug classes with preventable and non-preventable adverse drug events and associated level of severity

| Drug class | Severity (NCC MERP index), *n* (%) E (temporary patient harm) | F (prolonged hospitalisation and temporary harm) | G (permanent harm) | H (near-death) | Preventable ADEs, *n* (%) | Non-preventable ADE, *n* (%) | Total, *n* (%) |
|---|---|---|---|---|---|---|---|
| Central nervous system | 7 (50%) | 7 (50%) | 0 (0.00%) | 0 (0.00%) | 10 (27.8%) | 4 (15.4%) | 14 (22.6%) |
| Cardiovascular system | 6 (50%) | 2 (16.7%) | 2 (16.7%) | 2 (16.7%) | 9 (25%) | 3 (11.5%) | 12 (19.4%) |
| Anti-infectives | 10 (76.9%) | 1 (7.7%) | 2 (15.4%) | 0 (0.00%) | 5 (13.9%) | 8 (30.8%) | 13 (20.9%) |
| Total | (23/62, 37.1%) | (10/62, 16.1%) | (4/62, 6.5%) | (2/62, 3.2%) | (24/36, 66.7%) | (15/26, 57.7%) | (39/62, 62.9%) |

ADEs: adverse drug events.
NCC MERP: National Co-ordinating Council for Medication Error Reporting and Prevention.
E: Harm that required intervention and resulted in temporary patient harm.
F: Harm that required initial or prolonged hospitalisation and resulted in temporary patient harm.
G: Harm that resulted in permanent patient harm.
H: Harm that resulted in near-death event and required intervention to sustain life.

### 3.3 | Rate and nature of preventable adverse drug events

The majority of the confirmed ADEs were preventable (36/62, 58.1%). Few patients (5/302, 1.7%) experienced more than one preventable ADE. The estimated crude and adjusted (for follow-up period and PICU site) rates of preventable ADEs per 100 patients and 1000 patient-days are presented in Table 3.

The severity of confirmed preventable ADEs ranged between categories E (temporary harm to patient) through H (near-death event) on the NCC MERP index and most of these (21/36, 58.3%) fell into category E. Preventable ADEs were mostly associated with the

medicines prescribing stage (17/36, 47.2%) followed by the administration stage (13/36, 36.1%) (Table 4).

Medications for the central nervous system were the most common agents involved with preventable ADEs (10/36, 27.8%) followed by cardiovascular system agents (9/36, 25%) and medicines to treat infections (5/36, 13.9%) as shown in Table 5. Table S1 summarises drug classes involved with preventable ADEs, associated level of severity and explanation of their preventability.

### 3.4 | Associations between adverse drug events and covariates

In the univariate analysis, a significant association was only found between duration of follow -up and the occurrence of ADEs ($P < .001$) as shown in Table 6. In addition, PICU site was not associated with experiencing one or more ADEs before controlling for the other covariates ($P = .160$). Due to observed differences in patient characteristics (e.g., number of patients and age) between involved PICUs, we controlled for PICU site in the multivariate models to test the impact of these variations on ADE occurrence. PICU site was found to be significantly ($P = .006$) associated with ADE occurrence adjusting for the four independent variables involved in the multivariate logistic regression. Patients admitted to PICU-B (OR 0.27, 95% CI 0.10–0.69) or PICU-C (OR 0.26, 95% CI 0.10–0.65) were less likely to experience ADEs than those residing within PICU-A.

Another significant association was found between duration of follow-up and the occurrence of ADEs in the multivariate logistic analysis ($P < .001$). Patients who were screened for 1–2 weeks (OR 6.29, 95% CI 2.42–16.32) or more than 15 days (OR 13.12, 95% CI 5.01–34.34) were more likely to experience ADEs than those who were followed up for shorter periods (one week or less) as shown in Table 6.

Similarly, increased risk of a patient experiencing one or more preventable ADEs was only associated with duration of follow-up in the univariate analysis ($P < .001$). Duration of follow-up remained significantly associated with having preventable ADE ($P < .001$) in the multivariate logistic regression model (Table 6). Patients were more likely to experience preventable ADEs if they were followed up in PICUs for 7–14 days (OR 5.21, 95% CI 1.78–15.21) or more than 15 days (OR 8.02, 95% CI 2.68–23.96). PICU site was also found to be significantly associated with ADE occurrence in the multivariate analysis ($P < .033$). Patients in PICU-B (OR 0.40, 95% CI 0.14–1.08) and PICU-C (OR 0.26, 95% CI 0.09–0.74) were at lower risk of having preventable ADEs.

As longer stay in the ICU may result in a greater chance of experiencing an ADE, these regression models have been refitted excluding duration of follow-up (available on request) and no real difference to the associations with the other covariates was found.

The findings of the multinomial regression analysis support the logistic regression. Among the four independent variables, follow-up period was the only variable associated with the occurrence of both preventable ADEs and non-preventable ADEs identified in the univariate analysis ($P < .001$) as shown in Table 6.

Follow-up period remained significantly associated with ADE occurrence of both preventable ADEs and non-preventable ADEs after controlling for the other covariates ($P < .001$). The multivariate multinomial regression analysis also showed that PICU site was associated with occurrence of both preventable ADEs and non-preventable ADEs ($P < .017$).

## 4 | DISCUSSION

To our knowledge, this is the first UK-based study that has investigated the prevalence and nature of ADEs in critically ill children admitted to PICUs. This study found that ADEs are common in PICU patients and are more likely to occur in patients with longer PICU stay. One in six patients experienced one or more ADEs with an estimated rate of 20.5 per 100 patients and 16.7 per 1000 patient-days. Most of the identified ADEs were preventable (58.1%) at a rate of 9.43 per 1000 patient-days and associated commonly with the medicines prescribing stage. Medicines for the central nervous system, infections and the cardiovascular system were the most commonly involved drug classes. Nearly one third of identified ADEs (20/62, 32.3%) were classified as temporary harm, permanent harm and near-death events, which may have contributed to patients' prolonged hospitalisation.

We have observed significant variation in ADE rates between participating PICUs. This variation may be explained by differences between wards in terms of the unit size and variation in specialised care provided by centres (e.g., cardiac critical care). However, this variation in ADE rates prompts the need for further investigation to explore underlying factors between different PICUs that may influence the emergence of ADEs and the effective implementation of safety interventions. For example, there were stark differences in pharmacy service between the three study sites, which lead to pharmacists being available in the units at different times and on different days. Hence, addressing variations between centres is recommended, and organisations should evaluate their own local clinical practices to support successful implementation of national medication safety policies.[18]

A significant proportion of ADEs in this study were preventable with estimated rates of 11.7 per 100 patients and 9.43 per 1000 patient-days. Our rates are lower than those reported by single-site studies that collected ADE data prospectively originating from a PICU in the US (29 preventable ADEs per 1000 patient-days)[19] and a New Zealand NICU (14.38 per 1000 patient-days).[20] Lower rates of preventable ADEs have been reported in PICUs following a retrospective single site US study (2.3 preventable ADEs per 100 patients)[21] and across two Japanese NICUs (0.47 per 1000 patient-days).[22] However, a higher rate (21 preventable ADEs per 1000 patient-days) was reported by a US multicentre retrospective study.[23] Other studies utilised different methods of detecting ADEs such as voluntary incident report analysis and comparison was not practical,[24–27] varied in

**TABLE 6** Univariable and multivariable logistic regression analysis of adverse drug events

| Multivariable logistic regression analysis | | | | Multivariable multinomial logistic regression analysis | | |
|---|---|---|---|---|---|---|
| Covariate | Category | Odds ratios (95% CI) | *P*-value[a] | Category No ADEs (base outcome) | Coef. (95% CI) | *P*-value[a] |
| **Preventable and non-preventable ADEs** | | | | **Non-preventable ADEs** | | |
| Age | ≤29 days | Reference | 0.493 | ≤ (12 mo.)1 yr | Reference | 0.139 |
| | 1 mo. – 1 yr | 1.03 (0.35–3.03) | | 1 (>12 mo.) – 5 yr | 1.85 (0.38–3.32) | |
| | 1 (>12 mo.) – 5 yr | 2.21 (0.67–7.24) | | 5 (>60 mo.) – 12 yr | 0.26 (−1.58–2.11) | |
| | 5 (>60 mo.) – 12 yr | 0.99 (0.28–3.49) | | 12 (>144 mo.) – 18 yr | 2.02 (0.29–3.75) | |
| | 12 (>144 mo.) – 18 yr | 1.68 (0.41–6.75) | | | | |
| Follow-up period (days) | 1–6 | Reference | <0.001 | 1–6 | Reference | <0.001 |
| | 7–14 | 6.29 (2.42–16.32) | | 7–14 | 1.89 (0.11–3.68) | |
| | ≥15 | 13.12 (5.01–34.34) | | ≥15 | 3.01 (1.35–4.68) | |
| Number of medications on admission | 1–8 | Reference | 0.715 | 1–8 | Reference | 0.398 |
| | 9–13 | 1.33 (0.57–3.11) | | 9–13 | 1.54 (−0.14–3.23) | |
| | 14–23 | 1.4 (0.54–4.04) | | 14–23 | 1.02 (−0.83–2.89) | |
| Involved PICUs | PICU-A | Reference | 0.006 | PICU-A | Reference | 0.017 |
| | PICU-B | 0.27 (0.10–0.69) | | PICU-B | −1.79 (−3.45 – −0.13) | |
| | PICU-C | 0.26 (0.10–0.65) | | PICU-C | −0.97 (−2.36–0.41) | |
| **Preventable ADEs** | | | | **Preventable ADEs** | | |
| Age | ≤29 days | Reference | 0.981 | ≤ (12 mo.)1 yr | Reference | 0.139 |
| | 1 mo. – 1 yr | 0.75 (0.25–2.27) | | 1 (>12 mo.) – 5 yr | 0.19 (−0.09–1.34) | |
| | 1 (>12 mo.) – 5 yr | 0.75 (0.19–2.89) | | 5 (>60 mo.) – 12 yr | −0.08 (−1.2–1.04) | |
| | 5 (>60 mo.) – 12 yr | 0.72 (0.19–2.72) | | 12 (>144 mo.) – 18 yr | −0.41 (−2.0–1.23) | |
| | 12 (>144 mo.) – 18 yr | 0.63 (0.12–3.15) | | | | |
| Follow-up period (days) | 1–6 | Reference | <0.001 | 1–6 | Reference | <0.001 |
| | 7–14 | 5.21 (1.78–15.21) | | 7–14 | 1.77 (0.69–2.86) | |
| | ≥15 | 8.02 (2.68–23.96) | | ≥15 | 2.27 (1.14–3.40) | |
| Number of medications on admission | 1–8 | Reference | 0.604 | 1–8 | Reference | 0.398 |
| | 9–13 | 0.76 (0.29–2.02) | | 9–13 | −0.14 (−1.11–0.82) | |
| | 14–23 | 1.3 (0.42–4.06) | | 14–23 | 0.26 (−0.88–1.41) | |
| Involved PICUs | PICU-A | Reference | 0.033 | PICU-A | Reference | 0.017 |
| | PICU-B | 0.40 (0.14–1.08) | | PICU-B | −1.09 (−2.10 – −0.07) | |
| | PICU-C | 0.26 (0.09–0.74) | | PICU-C | −1.58 (−2.67 – −0.50) | |

PICUs: paediatric intensive care units, ADEs: adverse drug events.

[a]*P*-value is a 'composite' and represents the significance of the overall association between the covariate and the outcome (and not pairwise contrasts between the reference category and other individual categories).

definition,[28] examined only non-preventable ADEs[29] or reported ADE rates without clear denominator.[4] Standardised detection methods and definitions in future studies are, therefore, needed to allow direct comparison between estimates within and between countries.[30]

We have recently conducted a study to explore underlying contributory factors associated with medication-related incidents reported from PICUs across England and Wales between 2010 and 2018.[31] We found that the busy and pressurised working environment of the ICU, inadequate guidelines, staffing, systems and policies were commonly involved with harmful incidents. These organisation-related factors negatively affected the ability of health care staff to safely follow policies and procedures. Improvements in workload, and the redesign of processes and systems were identified as important strategies to mitigate harm associated with use of medicines in PICUs.

Medicines prescribing was commonly implicated with preventable ADEs in this study and in previous studies that examined medication errors in PICU.[10] Factors that contribute to prescribing errors in PICU have been explored recently in the UK.[32] Distractions and interruptions in the paediatric intensive care environment that contribute to mental fatigue of prescribers were found as potential factors that lead to prescribing errors. Hence, it was recommended that future interventions should consider mitigating cognitive load on prescribers and enhancing team performance to reduce such errors and associated harm.

Electronic prescribing systems may be a promising intervention to reduce prescribing errors in children's critical care.[33] Currently there is ongoing implementation and rollout of an electronic prescribing and administration system in UK hospitals, which is expected to reduced medication errors and ADEs by 50%.[34] However, such an intervention does not prevent all error types,[35] and should be supported by tailored Clinical Decision Support (CDS) systems for use in children.[36] In addition, involvement of clinical pharmacists in medication management processes such as validating prescriptions, participating in ward rounds and developing educational programmes for medical teams have yielded encouraging results in reducing medication errors in hospitalised children, including PICU patients.[37,38] However, the amount and quality of this evidence is still limited and further studies with robust controlled design evaluating the role of clinical pharmacy services on medication safety in children, particularly in those admitted to ICU, are warranted.[39]

High-risk medications such as anticoagulants, adrenergic antagonists and aminoglycosides were involved with preventable ADEs of a significant severity (permanent harm or near-death event) in this study.[40,41] Within the UK NHS context, all these medicines are subject to safe use guidelines. Therefore, there is a suggestion in this data that these are not having the desired effect. The continuing safe use of these drugs is, therefore, a clear target for ongoing medication safety improvement to reduce patient harm.

ADE have been associated with increased length of hospital stay and associated cost. It has been estimated that the cost of an ADE in ICU is around US$9000.[42] Nearly one third of identified ADEs in this study contributed to patient harm that caused prolonged patient stay in the PICU. In addition, we found that increased length of PICU stay was significantly associated with the risk of experiencing an ADE. These findings should be used to target efforts to reduce patient harm and associated costs on the health care system by reducing length of patient stay in PICU. There are ongoing initiatives to achieve this target in NHS hospitals, which have shown promising findings.[43,44] For example, a key component of the NHS five-year plan (2017) was reducing the number of delayed patients' discharge (including ICU patients) from hospitals.[44] Within two years of publishing this plan, around 2000 beds became available for new patients in NHS hospitals.[45]

This study has described rates of ADEs in critically ill paediatrics in the UK and added understanding of their clinical consequences. This work supports the national[46] and international[47] efforts to reduce preventable medication harm. It has examined multiple PICUs to enhance the generalisability of findings and utilised a prospective cohort design, using a standardised data collection method, which may help in detecting more ADEs than a retrospective design.[48] Additionally, this study did not apply any restrictions on the medications or type of events that could be recorded during the screening for ADEs, which helped in identifying a wide range of events. This study identified potential risk factors, high-risk medications involved with ADEs and unsafe medication practices that could be the focus of further research in PICUs (e.g., assessing the causes of ADEs). However, this study did not examine all possible factors (e.g., severity of illness and route of drug administration) that could be associated with the risk of ADEs in PICU and between study sites. A larger future study examining a wider range of factors could add further understanding.

Twelve of the 302 patients included in this study stayed in PICU for more than the 90-day study period; hence, the incidence rates may be overestimates. However, given that this only applies to 4% of patients, this will not have a significant effect on the calculated rate. In addition, eleven patients (3.6%) were affected by more than one ADE in this study. We acknowledge that we treated these as independent events (even though they might not have been) for analytical purposes, given that they were so few in number. If this had been more common, we would have needed to account for it using a multilevel model, which would account for the potential correlation of ADEs within patients.

Considering that the data collectors for this study were ward-based clinical pharmacists, errors that may have had the potential to cause ADEs were likely to have prompted intervention by pharmacists before reaching patients. For example, a rising level of creatinine is one of the signs that pharmacists would record and follow up to identify any actual harm (e.g., nephrotoxicity) that could be related to this trigger. Pharmacists would normally intervene and correct any medication error before it could cause any harm. This may result in a lower rate of preventable ADEs identified in this study. Additionally, variation between ADEs collected by different clinical pharmacists who participated in this study was expected. However, training data collectors on the standardised ADE detection method developed for this study, as well as the use of a multidisciplinary expert panel to review and confirm collected ADEs, were applied to enhance reliability of data.

## 5 | CONCLUSION

We report findings from the first prospective study to examine the frequency, nature, preventability and severity of ADEs in PICUs in the UK. We found that the risk of experiencing ADEs is significantly associated with increased length of PICU stay. The majority of identified ADEs were judged preventable and their consequences were often severe, resulting in patients' prolonged hospitalisation and temporary harm, permanent harm and near-death events. Increasing length of PICU stay, use of high-risk medications and prescribing practices and processes have been highlighted as targets for remedial interventions to reduce the risk of avoidable patient harm in this setting.

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### COMPETING INTERESTS

The authors state that they have no conflicts of interest that are directly relevant to the content of this study, and nor do they have financial relationships relevant to this article to disclose.

### CONTRIBUTORS

All authors contributed to the study conception and design. Material preparation was performed by A.A. and A.S., and analysis by A.A. and M.H. Data collection was performed by A.S., J.G., R.E.I. and A.A. The first draft of the manuscript was written by A.A. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### ETHICS APPROVAL

This study has been reviewed by the University of Manchester Research Ethics Committee (reference: 2018–5194-7250) and waived the need for ethical approval. This study was then reviewed and granted ethical approvals by the Health Research Authority (reference: NHS001521) and the Research and Development/Audit Departments from each participating NHS trust sites.

### CONSENT TO PARTICIPATE

Data utilised in this study were fully anonymised prior to being made available to the research team at the University of Manchester under ethical approval (reference: NHS001521) without individual consent from patients and practitioners.

### DATA AVAILABILITY STATEMENT

As per the ethical approval for this study (reference: NHS001521), access to data is only available after approval by the Health Research Authority and the Research and Development/Audit Departments from each participating NHS trust sites.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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