

# Epidemiology and potential risk factors of drug-related problems in Hong Kong paediatric wards

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The incidence of drug-related problems (DRPs) in hospitalized paediatric patients from countries other than Hong Kong is as high as 45.2%.
- Dosing and drug choice problems are the most frequent DRPs in children.
- There is no published research regarding the incidence and nature of DRPs in Hong Kong hospitalized children.

## WHAT THIS STUDY ADDS

- The incidence of DRPs is as high as 21.0% (95% confidence interval, 16.7–25.8%) in children hospitalized in Hong Kong.
- Of the DRPs in hospitalized children in Hong Kong, 81.7% were deemed preventable.
- The number of prescribed drugs per patient (five or more) and 'certain infectious and parasitic diseases' increased the risk of occurrence of DRPs.

## AIMS

A drug-related problem (DRP) is 'an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcome'. The extent and characteristics of DRPs in children in Hong Kong are unknown. The aim of this study was to determine the epidemiology of and identify risk factors for DRPs in hospitalized children in Hong Kong.

## METHODS

This was a prospective cohort study in children aged 0–18 years who were admitted to a medical ward, paediatric intensive care unit or neonatal intensive care unit of seven Hong Kong hospitals, during a 3 month period. Patients' charts, medical records and laboratory data were reviewed daily to identify DRPs; their preventability and severity were assessed. Logistic regression was used to analyse potential risk factors associated with the incidence of DRPs.

## RESULTS

Three hundred and twenty-nine children (median age, 2 years; interquartile range, 0 months to 9 years) were included. In total, 82 DRPs were experienced by 69 patients. The overall incidence of DRPs was 21.0% (95% confidence interval, 16.7–25.8%). The incidence was higher in neonatal and paediatric intensive care units than medical wards. Dosing problems were the most frequently reported DRPs ( $n = 35$ ; 42.7%), followed by drug choice problems ( $n = 19$ ; 23.2%) and adverse drug reactions ( $n = 11$ ; 13.4%). Sixty-seven (81.7%) DRP cases were assessed as preventable, 42 (51.2%) as minor and 40 (48.8%) as moderate. The number of prescribed drugs and 'certain infectious and parasitic diseases' were potential risk factors for occurrence of DRPs.

## CONCLUSIONS

Drug-related problems were common in hospitalized children in this study in Hong Kong; the most frequent were dosing and drug choice problems, and the majority of them were preventable. Polypharmacy and 'certain infectious and parasitic diseases' were potential risk factors.

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## Introduction

A drug-related problem (DRP) is defined as ‘an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes’ [1]. Addressing DRPs has become a priority, owing to the complexity of today’s drug therapy, which consequently makes appropriate drug prescribing increasingly challenging [2–4]. Previous studies have shown that DRPs in the paediatric population are of major concern [2, 5, 6].

Unrecognized and/or unresolved DRPs can potentially lead to significant drug-related morbidity and/or mortality [7]. Hospitalizations, long-term care admissions, emergency department visits, additional physician office visits and additional prescriptions are some of the consequences associated with DRPs [8]; therefore, the economic burden of DRPs is extensive, and this has been reported previously [8].

Although epidemiological and economic data of DRPs in the paediatric population are still limited, a recent study from the UK and the Kingdom of Saudi Arabia that investigated DRPs in hospitalized children found that 45.2% ( $n = 333$  of 737) of paediatric patients experienced DRPs, 80.3% of which were assessed as preventable [2]. Data from other countries are still lacking. Medications used and the healthcare systems in different countries can vary significantly; consequently, the types of drug-related problems can be different. Hence, different strategies in the reduction of DRPs may be needed in different countries.

Hong Kong Hospital Authority (HA) is currently consolidating the paediatric services, and a new paediatric hospital is being built. The Chief Pharmacist Office of HA is responsible for designing future strategies to optimize the use of medicines and reduce DRPs. Epidemiological data on DRPs in hospitalized paediatric patients in Hong Kong were lacking; therefore, the Chief Pharmacist Office co-ordinated this study in order to determine the epidemiology of DRPs and identify potential associated risk factors for DRPs in children admitted to hospitals in Hong Kong.

## Methods

### Study design and population

We used the same methodology as reported previously by Rashed *et al.* [2], which is summarised below.

An observational study was conducted in seven large hospitals in Hong Kong. Patients included were children aged 0–18 years and admitted to the medical wards, paediatric intensive care units (PICUs) and neonatal intensive care units (NICUs). Data were collected by the staff pharmacists (seven pharmacists from seven hospitals) on a daily basis (excluding weekends) over a 3 month period (from June 2009 to September 2009) for all wards using a modified version of the DRP-Registration Form

version 5.01 designed by the Pharmaceutical Care Network Europe [1], as used in the previous study [2]. A DRP was defined as ‘an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes’ [1]. All identified DRPs were classified using the Pharmaceutical Care Network Europe classification system (version 5.01) [1]. All potential DRPs detected by the staff pharmacists were peer reviewed by an expert panel, which consisted of three consultant paediatricians. The members of the panel assessed the severity of the identified DRPs independently using a previously published validated scale [9].

The preventability of all identified DRPs from the seven hospitals was assessed by two reviewers (clinical pharmacist and consultant paediatrician) using the criteria provided by Schumock and Thornton [10].

Severity and preventability criteria were presented in detail in a previous study by Rashed *et al.* [2].

For standardization, established international terminologies were used, i.e. Anatomic Therapeutic Chemical (ATC) classification (WHO-ATC) [11] for drugs and International Classification of Diseases version 10 (WHO-ICD 10) [12] for diagnoses.

Children were grouped into five age groups modified from the International Conference of Harmonization Guideline E11 as follows:  $\leq 1$  month;  $> 1$  month to  $\leq 2$  years;  $> 2$  to  $\leq 6$  years;  $> 6$  to  $\leq 12$  years; and  $> 12$  to  $\leq 18$  years [13].

### Incidence of drug-related problems

The incidence of patients with a DRP was defined as the number of patients with at least one DRP during the study period divided by the total number of patients in the study cohort multiplied by 100 or by the total number in each of the wards across all hospitals, as appropriate. The incidence was calculated with 95% confidence intervals (CIs).

### Statistical analysis

The data were entered into Microsoft Access 2007 and analysed using Stata 11 (StataCorp, College Station, TX, USA). Descriptive statistics were performed on all data. Data are presented as number, percentage, median, interquartile range (IQR; Q1–Q3) unless otherwise specified. Chi-squared test, Kruskal–Wallis rank and Wilcoxon rank sum (Mann–Whitney  $U$  test) were used as appropriate. For all tests,  $P < 0.05$  was selected as the level for statistical significance.

To identify the independent predictors of DRP occurrence (dependent variable), logistic regression analysis was conducted. Based on the univariable analysis, the variables that were significant were included in the full model; these were gender, age (in groups), ‘certain infectious and parasitic diseases’, number of prescriptions per patient (grouped as  $< 5$  or  $\geq 5$ ), and type of admission (emergency, scheduled or transferred). Results are reported as odds ratios (ORs) with 95% CIs.

**Table 1**

Patients' demographics in each ward and overall

	Medical (n = 219)*	NICU (n = 74)*	PICU (n = 36)*	Total (n = 329)*
Gender [n (%)]				
Female	88 (40.2)	36 (48.6)	14 (38.9)	138 (41.9)
Male	131 (59.8)	38 (51.4)	22 (61.1)	191 (58.1)
Median age (IQR, Q1–Q3)	4 years (0–12 years)	6 days (3–14 days)	4 years (0–9.5 years)	2 years (0–9 years)
No. of patients by age group [n (%)]				
0–1 month	15 (6.8)	61 (82.4)	0	76 (23.1)
>1 month to ≤2 years	45 (20.5)	13 (17.6)	14 (38.9)	72 (21.9)
>2 to ≤6 years	63 (28.8)	0	9 (25.0)	72 (21.9)
>6 to ≤12 years	42 (19.2)	0	7 (19.4)	49 (14.9)
>12 to ≤18 years	54 (24.7)	0	6 (16.7)	60 (18.2)

Abbreviations are as follows: IQR, interquartile range; NICU, neonatal intensive care unit; and PICU, paediatric intensive care unit. \*n is the total number of patients.

Age and gender were included in the full model although they were not significant in the univariable analysis, because previous studies had identified them as risk factors for adverse drug reactions (ADRs) and medication errors [14, 15].

### Ethical approval

Ethical approval was not considered necessary because this was an observational study. However, it was approved by the Hong Kong Hospital Authority Paediatric Coordinating Committee, approval number [(67) in PHS 01/53 (II)].

## Results

### Characteristics of study population

A total of 329 patients were included in this study from the seven hospitals in Hong Kong. Their age ranged from 0 to 18 years (median, 2 years; IQR, 0–9 years), and 58.1% (n = 191) were male. Table 1 gives details of patients' characteristics in each ward as well as in the overall study cohort.

Using the WHO-ICD 10 classification, the most frequently reported diagnoses (conditions) the children had were 'diseases of the respiratory system' (n = 70), followed by 'certain conditions originating in the perinatal period' (n = 66; Appendix S1 shows the diagnoses most frequently reported in the study cohort).

### Incidence of drug-related problems

A total of 82 DRPs were identified for 69 children (Table 2). The overall incidence of DRPs in the study cohort was 21.0% (95% CI, 16.7–25.8%). The highest incidences were reported from the NICUs (25.7%; 95% CI, 16.2–37.2%) and PICUs (25.0%; 95% CI, 12.1–42.2%; Table 2). Overall, no significant difference in DRP incidence was found between age groups, between gender (P = 0.157) or between wards (P < 0.366). In NICUs, the percentage of male patients with

DRPs was higher than for female patients (34.2 vs. 16.7%), although the difference was not significant (P = 0.084).

### Types of drug-related problems

Dosing problems had the highest frequency amongst the reported problems (n = 35; 42.7%), followed by drug choice problems (n = 19; 23.3%). This was the case in each of the three wards in the study cohort. Adverse drug reactions (n = 11; 13.4%) were the third most frequently reported type of DRP. The incidence of patients with ADRs among the total study population was 3.0% (n = 9 of 329). A summary of the most common DRPs in the six main categories and related subcategories is given in Table 3.

### Drugs involved in the occurrence of drug-related problems

In total, 1474 prescriptions were recorded in the study cohort. Using the WHO-ATC classification system for medications, the ATC anatomical groups (first level) most often prescribed were 'systemic anti-infectives' (J; n = 341 of 1474; 23.1%), 'nervous system' drugs (N; n = 334 of 1474; 22.6%), 'alimentary tract and metabolism' (A; n = 272 of 1474; 18.4%), 'respiratory system' drugs (R; n = 135 of 1474; 9.2%) and 'blood and blood forming organs' drugs (B; n = 110 of 1474; 7.5%). These groups were the groups most often involved in the DRPs, with group J having the highest percentage (8.0%; n = 27 of 341), followed by group B (7.3%; n = 8 of 110), group A (5.1%; n = 14 of 272), group R (3.7%; n = 5 of 135) and group N (3.0%; n = 10 of 334).

Gentamicin, ranitidine and fluconazole were most frequently associated with DRPs [n = 4 (4.9%) cases, each], followed by nystatin (n = 3 cases; 3.7%) and caffeine (n = 2 cases; 2.4%). These drugs were mainly reported from NICUs.

### Causes

Overall, 119 causes were reported for the 82 identified DRPs. The majority (n = 47; 39.5%) were related to the

**Table 2**

Frequency of drug-related problems and incidence of patients with drug-related problems in each ward and overall

	Medical (n = 219)*	NICU (n = 74)*	PICU (n = 36)*	Total (n = 329)*
No. of DRPs (%)	47 (57.3)	26 (31.7)	9 (11.0)	82 (100)
No. of patients with DRPs [n (%)]	41 (18.7)	19 (25.7)	9 (25.0)	69 (21.0)
No. of patients with DRPs by gender [n (%)]				
Female	16 (18.2)	6 (16.7)	4 (28.6)	26 (18.8)
Male	25 (19.1)	13 (34.2)	5 (22.7)	43 (22.5)
No. of patients with DRPs, stratified by DRP type [n (%)]†				
Dosing problem	20 (48.8)	11 (57.9)	4 (44.4)	35 (50.7)
Drug choice problem	7 (17.1)	10 (52.6)	2 (22.2)	19 (27.5)
Adverse drug reactions	9 (21.9)	2 (10.5)	0	11 (15.9)
Drug use problem	6 (14.6)	1 (5.3)	0	7 (10.1)
Others	4 (9.8)	2 (10.5)	1 (11.1)	7 (10.1)
Interactions	1 (2.4)	0	2 (22.2)	3 (4.3)
DRP incidence [% (95% confidence interval)]	18.7 (13.8–24.5)	25.7 (16.2–37.2)	25.0 (12.1–42.2)	21.0 (16.7–25.8)

Abbreviations are as follows: DRP, drug-related problem; NICU, neonatal intensive care unit; and PICU, paediatric intensive care unit. \*n is the total number of patients. †Numbers of patients in various DRP type categories do not add up to the total number of patients with DRPs in each ward, because one child can contribute to more than one DRP type; the percentage is calculated as the number of patients with DRP divided by total number of patients in each ward or in the total study cohort, as appropriate.

**Table 3**

The most common type of drug-related problems identified in the study cohort\*

Category of drug-related problem	Detailed classification	Total [n (% of 82)]	
Dosing problem	Total	35 (42.7)	
	Drug dose too low or dosing interval too long	16 (19.5)	
	Drug dose too high or dosing interval too short	13 (15.9)	
	Duration of treatment too long	3 (3.7)	
Drug choice problem	Total	19 (23.2)	
	Inappropriate drug	7 (8.5)	
	No clear indication for drug	6 (7.3)	
	No drug but clear indication	3 (3.7)	
Adverse reactions	Total	11 (13.4)	
	Side-effect suffered (non-allergic)	9 (11.0)	
	Drug use problem	Total	7 (8.5)
		Drug not taken/administered at all	7 (8.5)
Others	Total	7 (8.5)	
	Insufficient awareness of health and disease	6 (7.3)	
Interactions	Total	3 (3.7)	
	Potential interaction	2 (2.4)	

\*Classified according to Pharmaceutical Care Network Europe classification version 5.01.

selection of the drug and/or dosage. The next most frequent causes involved the drug use process (e.g. inappropriate timing of dosing; n = 26; 21.8%), followed by patient/psychological causes (e.g. caregiver suspects side-effects; n = 20; 16.8%). Table 4 shows the most frequently reported causes of DRPs.

### Interventions

Overall, 145 interventions were necessary to manage the 82 identified DRPs (median, two per DRP). A total of 72 (49.7% of all interventions) were at prescriber level, followed by interventions at drug level (n = 51; 35.2% of all interventions), while only 17 (11.7%) interventions were at patient/caregiver level (Table 4).

### Classification of severity

Overall, the majority of the DRPs were found to be minor (n = 42; 51.2%) in severity, and 40 (48.8%) DRPs were assessed as moderate. This was similar at ward level except for PICUs, where the majority of the cases (n = 8; 88.9% of nine cases) were assessed as moderate in severity.

### Preventability

Overall, most of the identified DRPs (n = 67; 81.7%) were found to be preventable; this was similar in each of the wards [medical, n = 33 (70.2%); NICU, n = 25 (96.2%); and PICU, n = 9 (100%)]. Most of the preventable DRPs were associated with dosing problems (47.8%; n = 32 of 67) and drug choice problems (25.4%; n = 17 of 67). All interaction cases (n = 3) were deemed preventable.

### Factors associated with occurrence of drug-related problems

The univariable analysis showed three predictors that were significantly associated with DRP occurrence (Table 5). In the full model, however, only two predictors remained significant. A patient was more likely to experience a DRP if the average number of prescribed drugs per patient was ≥5 and/or the patient was diagnosed with ‘certain infectious and parasitic diseases’.

**Table 4**

The most frequently reported causes of drug-related problems and the interventions taken in the study cohort\*

Main category/ subcategory		Total	
Causes [n (% of 119†)]	Drug or dose selection	47 (39.5)	
	Inappropriate dosage selection	20 (16.8)	
	Inappropriate drug selection	8 (6.7)	
	Deterioration of disease state	7 (5.9)	
	Manifest side-effect	4 (3.4)	
	Drug use process	26 (21.8)	
	Drug underused/underadministered	9 (7.6)	
	Drug overused/overadministered	7 (5.9)	
	Inappropriate timing of dosing	6 (5.0)	
	Patient/psychological	20 (16.8)	
	Caregiver suspects side-effects	7 (5.9)	
	Caregiver has concerns with drugs	6 (5.0)	
	Information	8 (6.7)	
	Instructions for use/taking not known	4 (3.4)	
	Lack of communication between health professionals	3 (2.5)	
	Logistics	9 (7.6)	
	Other prescribing error (information wrong/missing on the prescription)	8 (6.7)	
	Interventions [n (% of 145‡)]	At prescriber level	72 (49.7)
		Intervention proposed, approved by prescriber	42 (29.0)
Prescriber informed only		8 (5.5)	
Intervention proposed, not approved by prescriber		6 (4.1)	
At patient/carer level		17 (11.7)	
Patient counselling		9 (6.2)	
Spoken to family member/caregiver		7 (4.8)	
At drug level		51 (35.2)	
Dosage changed		22 (15.2)	
Drug changed		9 (6.2)	
Drug stopped		8 (5.5)	
New drug started		4 (2.8)	
Instruction for use changed		3 (2.1)	

\*Classified according to Pharmaceutical Care Network Europe classification version 5.01. †Total number of causes reported. ‡Total number of interventions reported.

## Discussion

The incidence and nature of all types of DRPs in hospitalized children in Hong Kong has not been studied previously. This study showed that DRPs were frequent in hospitalized paediatric patients in Hong Kong and that the majority of the DRPs could be prevented by healthcare professionals. Twenty-one per cent (95% CI, 16.7–25.8%) of the hospitalized children included in this study experienced at least one DRP.

### Epidemiology of drug-related problems

*Types and causes of drug-related problems* In this study, the majority of DRPs reported were related to dosing and drug choice problems. Adverse drug reactions were the third most frequent type of DRP. These results are similar

to the findings of our previous study in the UK and the Kingdom of Saudi Arabia [2]. Overall, the incidence of patients experiencing an ADR in this study was 3.0% (95% CI, 1.3–5.1%). This is very low compared with the incidence of ADRs in Hong Kong reported in the only published study (ADVISE), which investigated the incidence of ADRs in hospitalized paediatric patients in five countries, including Hong Kong [16]. The ADVISE study found the incidence of ADRs in Hong Kong to be as high as 10.3% (95% CI, 5.5–17.4%). There are a few possible explanations for such a difference between the two studies. The total number of patients from Hong Kong included in ADVISE was small ( $n = 143$ ), and they were from one medical ward of a single hospital. Furthermore, in the ADVISE study the researchers were focused on identifying ADRs, whereas the present study was looking for all DRP types; thus, ADRs may have been underdetected or there may have been differences in documentation across the seven hospitals included in this study. However, the highest number of patients reported to have ADRs in our present study was from the medical wards, which is consistent with the ADVISE study.

*Drugs involved in drug-related problems* The three drug groups that were most frequently involved in DRP cases were 'systemic anti-infective', 'alimentary tract and metabolism' and 'nervous system' drugs. These findings are in line with previous paediatric studies in other countries [2].

Gentamicin, fluconazole and ranitidine were the drugs most frequently associated with DRPs and were mainly reported from the NICUs. In contrast, in the UK and Kingdom of Saudi Arabia study, the most frequently involved antibiotics were 'amoxicillin & enzyme inhibitor', which were mainly reported in the medical wards [2].

*Preventability and severity* In the present study, most of the identified DRPs ( $n = 67$  of 82; 81.7%) were deemed preventable, similar to the previous study ( $n = 384$  of 478; 80.3%) [2]. Regarding severity of identified DRPs, most were found to be minor in severity ( $n = 42$  of 82; 51.2%). However, the percentage of DRPs assessed as being moderate in severity ( $n = 40$  of 82; 48.8%) was relatively high compared with the previous study conducted in UK and Kingdom of Saudi Arabia, where 27% (129 of 478) were assessed as moderate [2].

*Interventions* Changing the dose and changing the drug were the most common interventions in this study. This was similar to the previous study [2]. Concern with regard to the limitation of paediatric pharmacology and pharmacotherapy training within medical and nursing professions has been recognized [2]; therefore, providing more training in prescribing to these health professionals is of great importance [17].

**Table 5**

Potential risk factors for DRPs in the total study

Risk factors	Univariable odds ratio (95% confidence interval)	P value	Full model* odds ratio (95% confidence interval)	P value
Gender (female vs. male)	0.8 (0.5–1.4)	0.420	0.7 (0.4–1.3)	0.262
Age (in group)				
0–1 month	1.0 (reference)		1.0 (reference)	
>1 month to ≤2 years	0.7 (0.3–1.5)	0.307	1.3 (0.5–3.8)	0.606
>2 to ≤6 years	0.6 (0.3–1.3)	0.216	1.8 (0.5–6.8)	0.364
>6 to ≤12 years	0.9 (0.4–2.0)	0.745	2.1 (0.5–7.8)	0.289
>12 to ≤18 years	0.9 (0.4–2.0)	0.822	2.5 (0.7–8.7)	0.166
Diagnosis A00–B99 (yes/no)†	3.0 (1.1–7.7)	0.03	3.2 (1.2–8.9)	0.024
Average number of prescriptions (≥5 vs. <5)	1.9 (1.1–3.4)	0.02	2.2 (1.3–4.0)	0.006
Type of admission				
Emergency	1.0 (reference)		1.0 (reference)	
Scheduled	2.0 (1.1–3.7)	0.022	2.0 (0.9–4.1)	0.078
Transferred	1.8 (0.8–3.9)	0.140	1.5 (0.6–3.4)	0.385

\*Full model adjusted by ward. †A00–B99, ‘certain infectious and parasitic diseases’ (e.g. acute encephalitis).

**Risk factors** The logistic regression analysis showed that the number of drugs prescribed per patients (≥5 prescribed drugs) and presence of ‘certain infectious and parasitic diseases’ were strong predictors for DRP occurrence. Polypharmacy was also a strong predictor for overall DRP occurrence in a previous study in the UK and the Kingdom of Saudi Arabia [2].

Infectious diseases, such as gastroenteritis or other viral infections, are relatively common in children in Asia, where weather is usually hot and humid. These children may be more likely to be prescribed more medications. However, as other studies investigating paediatric DRPs and the association of diseases with their incidence are limited, it is difficult to make comparisons with our results.

### Strengths and limitations

To our knowledge, this is the first study to quantify the occurrence of and investigate the potential risk factors of all types DRPs in children admitted to paediatric wards in Hong Kong, indeed in South-East Asia. This study was conducted in seven hospitals in Hong Kong, using standardized methods for data collection, and was of a substantial size. Also, the methodology used (chart review) has been recognized as the gold standard in pharmacoepidemiology and has been well tested in European countries (EU) as well as the USA [18, 19].

Certain limitations must be considered when interpreting our findings. Unlicensed and/or off-label use of medication in children was not considered in the analysis as a potential risk factor of DRPs. Also, inter-rater reliability to evaluate the agreement between the staff pharmacists from the seven hospitals on identifying DRPs was not conducted, and this should be considered for future work.

### Future research

In this study, a difference between genders was identified with regard to the percentage of children with DRPs in the NICUs; thus, future work to look for more detailed information on drug usage in these wards would be interesting and could add to the knowledge of medication usage in neonates.

Although none of the DRPs was classified as severe, it is currently not known how nonsevere (mild/moderate) DRPs affect the care of the children. Further studies should be conducted to evaluate the potential consequences of these DRPs.

Finally, the US and EU governments have recognized the importance of medicines for children. These governments have invested a large amount of resources and implemented regulations to build appropriate environments for the research and development of medicines for children and for monitoring the safety of their use. However, such initiatives have not been seen in South-East Asia, and more research into the use and safety of medicines for children in this region is definitely needed.

### Conclusions

This study showed the extent of DRPs in hospitalized children in Hong Kong, and they were common. Dosing and drug choice problems were the DRPs most often identified. Also, the study showed that if the number of prescribed drugs per patient was ≥5 and if the patient had ‘certain infectious and parasitic diseases’, the risk of DRPs was increased. ‘Anti-infectives’ and ‘alimentary tract and metabolism’ were the drug groups most often associated with DRPs. Also, a high percentage of identified DRPs was assessed as preventable. There are limited data in South-East Asia about paediatric medication

usage; this study has highlighted the need for more local research.

## Competing interests

There are no competing interests to declare.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

### Appendix S1

Ten most frequent diagnoses using WHO-ICD10 classification