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Application of a Common Data Model (CDM) to rank the paediatric user and prescription prevalence of 15 different drug classes in South Korea, Hong Kong, Taiwan, Japan and Australia: an observational, descriptive study

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ABSTRACT

Objective To measure the paediatric user and prescription prevalence in inpatient and ambulatory settings in South Korea, Hong Kong, Taiwan, Japan and Australia by age and gender. A further objective was to list the most commonly used drugs per drug class, per country.

Design and setting Hospital inpatient and insurance paediatric healthcare data from the following databases were used to conduct this descriptive drug utilisation study: (i) the South Korean Ajou University School of Medicine database; (ii) the Hong Kong Clinical Data Analysis and Reporting System; (iii) the Japan Medical Data Center; (iv) Taiwan's National Health Insurance Research Database and (v) the Australian Pharmaceutical Benefits Scheme. Country-specific data were transformed into the Observational Medical Outcomes Partnership Common Data Model.

Patients Children (≤18 years) with at least 1 day of observation in any of the respective databases from January 2009 until December 2013 were included.

Main outcome measures For each drug class, we assessed the per-protocol overall user and prescription prevalence rates (per 1000 persons) per country and setting.

Results Our study population comprised 1 574 524 children (52.9% male). The highest proportion of dispensings was recorded in the youngest age category (<2 years) for inpatients (45.1%) with a relatively high user prevalence of analgesics and antibiotics. Adrenergics, antihistamines, mucolytics and corticosteroids were used in 10%–15% of patients. For ambulatory patients, the highest proportion of dispensings was recorded in the middle age category (2–11 years, 67.1%) with antibiotics the most dispensed drug overall.

Conclusions Country-specific paediatric drug utilisation patterns were described, ranked and compared between four East Asian countries and Australia. The widespread use of mucolytics in East Asia warrants further investigation.

Strengths and limitations of this study

- We conducted the largest Western Pacific paediatric drug utilisation study to date using a Common Data Model, which allowed us to rank the user and prescription prevalence of 15 different drug classes in South Korea, Hong Kong, Taiwan, Japan and Australia.
- Our comprehensive overview of country-specific pharmacological agents used in both an ambulatory and inpatient setting, by gender and age, included data of 1 574 524 children and identified important differences in drug paediatric utilisation patterns.
- Despite the differences in databases in terms of setting and study populations, we believe our overview of prescription patterns and rankings is an important step to further investigate and facilitate the rational use of drugs in paediatric populations in East Asia and Australia.
- Over the counter prescribing in individual countries was not captured and we may have underestimated the true drug utilisation of agents, such as paracetamol and some antihistamines.
- We collected data until the end of 2013 and acknowledge that, due to the rapid change in paediatric licensing of therapeutic agents, some of our findings might be worthwhile replicating with more current data.

INTRODUCTION

An important step to facilitate the rational use of drugs in paediatric populations is to investigate drug utilisation patterns.[1] Observational data in the form of electronic health records (EHR) and insurance claims data, real-life data, have been used successfully to investigate the use of drugs in children.[1–3] European studies on paediatric drug

utilisation patterns have shown that the most commonly used drugs in European children include anti-infective, respiratory and dermatological drugs and are largely prescribed off-label.[3] While drug-specific paediatric drug utilisation data from East Asian countries are available,[4–6] a comprehensive overview of the most commonly used drugs is currently lacking.

The Asian Pharmacoepidemiology Network, the first multinational research network in Asia, in collaboration with the Observational Medical Outcome Partnership (OMOP) set up an initiative to convert domestic databases in Asian countries to a Common Data Model (CDM) to offer a multinational research infrastructure to facilitate studies.[7 8] We used this network of observational healthcare databases in South Korea, Hong Kong, Taiwan, Japan and Australia to measure and compare the prevalence of drug prescribing in East Asian and Australian children. Our primary aim was to measure the paediatric user and prescription prevalence in inpatient and ambulatory settings in the five aforementioned countries by age and gender. A further objective was to list the most commonly used drugs per drug class, per country, in both an inpatient and ambulatory setting.

METHODS

Data sources

We conducted a drug utilisation study using paediatric patient populations from the following databases: (i) Ajou University School of Medicine (AUSOM) from South Korea; (ii) the Hong Kong Clinical Data Analysis and Reporting System (CDARS); (iii) the Japan Medical Data Center (JMDC); (iv) Taiwan's National Health Insurance Research Database (NHIRD) and (v) the Australian Pharmaceutical Benefits Scheme (PBS). All data were anonymised to protect patient confidentiality.

All five countries have universal healthcare systems and none of the databases include information on patients using private healthcare.[7] The South Korean and Hong Kong databases, AUSOM and CDARS, collect and archive the EHR of hospital inpatients. Briefly, AUSOM is an EHR database of a Korean teaching hospital providing both secondary and tertiary care, with 1096 patient beds and 23 operating rooms with data for over 2 073 120 individuals, collected since 1994. By contrast, CDARS contains secondary care data from *all* public hospitals in Hong Kong and their associated ambulatory and primary care clinics since 1995.[9–11] The database was developed and is maintained by the Hong Kong Hospital Authority, a statutory body providing healthcare services available to all Hong Kong residents (over 7 million) and covering about 80% of all hospital admissions.

The Japanese, Taiwanese and Australian data were extracted from insurance research databases. The Japanese JMDC comprises data from 60 Society-Managed Health Insurances covering workers aged 18–65 years and their dependents (children and elderly).[12] The monthly claims data are derived from claims issued by clinics, hospitals and community pharmacies from July 2009 onwards. Australian data consist of national pharmacy claims data from the Australian Government Department of Human Services which provides information of medicines subsidised and dispensed under the Pharmaceutical Benefits Scheme. PBS data are collected from pharmacies and private hospitals, and discharge or outpatient dispensing from public hospitals, but do not include inpatient public hospital prescriptions. From Taiwan, we extracted reimbursement data from the Bureau National Health Insurance (NHI) system, which has registered all medical claims since 1995. More than 99% of the citizens of Taiwan are enrolled in the NHI, which offers mandatory and comprehensive medical care coverage to all Taiwanese residents.

Information on specific indications of drug use was not available in the datasets from Hong Kong, Taiwan and Japan. Further details of each database have been described elsewhere.[13]

Data collection

For this retrospective descriptive study, we identified children, 18 years or younger, with at least 1 day of observation in any of the respective databases. The follow-up period for all children started in January 2009 or the start date of observation, whichever was last. Follow-up ended in December 2013, the last date observation or the date a child turned 18, whichever was first. Specifically, observation time was defined as: 1) the start of the first visit (inpatient, outpatient or emergency room) to the end of the last visit for the Korean AUSOM database; 2) the date of birth until death in the Hong Kong CDARS database and 3) the insurance enrolment date in the Japan JMDC, Taiwan NHIRD and Australian PBS. Data were available from the end of 2009 onwards for the Japanese JMDC and until December 2011 for the Taiwanese database (NHIRD). We used randomly selected samples from CDARS, NHIRD and PBS as only ~10% of the total data were made available for research.

Data extraction

Data extraction, a population file with information on demographics and dispensing records, was performed through a shared analysis programme combining R and SQL. This programme was distributed to the data partners, executed locally against the data in OMOP CDM format and results were returned to the central coordinating site (University of Hong Kong). Both the extraction software and the analysis code are available as open source: https://github.com/OHDSI/StudyProtocols/tree/master/DrugsInPeds

Each database's full set of drug codes were mapped to RxNorm concepts using a semi-automated process; using known ATC codes for each code, a set of one or more RxNorm ingredients was identified based on the OMOP Standardised Vocabularies link between ATC and RxNorm. In case of ambiguity, manual adjudication was used to select the appropriate RxNorm ingredient.

Table 1 Patient characteristics, person years and number of prescription by age and calendar year

	Korea (AUSOM) (n=220 076)	Hong Kong (CDARS)* (n=18 634)	Japan (JMDC) (n=913 006)	Taiwan (NHIRD) (n=235 214)	Australia (PBS) (n=187 594)
Total number of person years	259 750	71 502	3 006 825	630 051	774 420
Gender (number of children/number of person years (%))					
Female	98 921/115 868 (44.61)	8 389/31 433 (43.96)	433 918/1 459 304 (48.53)	113 179/301 824 (47.90)	87 129/360 099 (46.50)
Male	121 155/143 882 (55.39)	9 656/36 875 (51.57)	479 088/1 547 521 (51.47)	122 035/328 226 (52.10)	100 465/414 322 (53.50)
Age (number of children/number of person years (%))					
<2 years	69 121/32 909 (12.7)	5 758/7937 (11.1)	175 070/304 672 (10.1)	31 659/42 445 (6.7)	62 021/86 181 (11.1)
2–11 years	122 177/152 352 (58.7)	11 120/34 767 (48.6)	448 008/1 613 909 (53.7)	133 727/305 543 (48.5)	138 714/462 755 (59.8)
12–18 years	60 230/74 489 (28.7)	9 458/28 798 (40.3)	348 343/1 088 244 (36.2)	131 969/282 063 (44.8)	86 051/225 484 (29.1)
Calendar year (number of children/number of person years (%))					
2009	109 462/72 472 (27.9)	14 797/14 148 (19.8)	519 973/311 734 (10.4)	228 059/216 660 (34.4)	165 735/149 157 (19.3)
2010	101 055/66 090 (25.4)	14 843/14 147 (19.8)	573 486/644 681 (21.4)	221 661/211 666 (33.6)	168 702/152 689 (19.7)
2011	93 416/57 515 (22.1)	15 001/14 274 (20.0)	590 384/665 955 (22.2)	208 643/201 725 (32.0)	171 233/155 597 (20.1)
2012	83 504/44 161 (17.1)	15 215/14 459 (20.2)	594 331/686 775 (22.8)		172 842/158 117 (20.4)
2013	51 575/19 512 (7.5)	15 182/14 475 (20.2)	589 192/697 680 (23.2)		173 286/158 861 (20.5)
Number of drugs dispensed (inpatient)					
Total	3 126 567	48 166	5 311 981	361 985	–
<2 years, n (%)	1 354 036 (43.3)	17 816 (37.0)	2 523 959 (47.5)	92 518 (25.6)	–
2–11 years, n (%)	1 158 851 (37.1)	12 852 (26.7)	1 980 742 (37.3)	156 401 (43.2)	–
12–18 years, n (%)	613 680 (19.6)	17 498 (36.3)	807 280 (15.2)	113 066 (31.2)	–
Number of drugs dispensed (ambulatory)					
Total	–		19 511 710	23 520 356	1 620 805
<2 years, n (%)	–		1 346 903 (6.9)	2 880 951 (12.2)	187 486 (11.5)
2–11 years, n (%)	–		14 036 081 (71.9)	14 984 130 (63.7)	950 984 (58.7)
12–18 years, n (%)	–		4 128 726 (21.2)	5 655 275 (24.0)	482 335 (29.8)

*For 589 children in CDARS gender was not recorded at admission.
AUSOM, the South Korean Ajou University School of Medicine; CDARS, the Hong Kong Clinical Data Analysis and Reporting System; JMDC, the Japan Medical Data Center ; NHIRD, Taiwan's National Health Insurance Research Database; PBS, the Australian Pharmaceutical Benefits Scheme .

Table 2 User prevalence and prescription prevalence and in an inpatient setting by therapeutic level: prevalence per 1000 persons

	Korea (AUSOM)		Hong Kong (CDARS)		Japan (JMDC)		Taiwan (NHIRD)	
Class*	User prevalence (%)†	Prescription prevalence (%)‡	User prevalence (%)†	Prescription prevalence (%)‡	User prevalence (%)†	Prescription prevalence (%)‡	User prevalence (%)†	Prescription prevalence (%)‡
Analgesics (including NSAIDs)	109 (23)	1269 (23)	131 (36)	314 (19)	31 (19)	380 (24)	43 (25)	195 (23)
Antibiotics	107 (22)	1141 (20)	91 (25)	634 (37)	43 (26)	496 (31)	37 (21)	233 (27)
Adrenergics	65 (14)	520 (9)	31 (9)	101 (6)	23 (14)	161 (10)	23 (13)	110 (13)
Antihistamines	53 (11)	520 (9)	55 (15)	136 (8)	11 (7)	48 (3)	23 (13)	77 (9)
Mucolytics	53 (11)	614 (11)	4 (1)	7 (0)	22 (13)	168 (11)	19 (11)	69 (8)
Corticosteroids	45 (9)	425 (8)	21 (6)	89 (5)	15 (9)	89 (6)	18 (10)	72 (8)
Anti-infectives (excluding antibiotics and vaccines)	9 (2)	130 (2)	14 (4)	48 (3)	2 (1)	28 (2)	2 (1)	15 (2)
Antiepileptics	8 (2)	431 (8)	3 (1)	36 (2)	2 (1)	27 (2)	2 (1)	23 (3)
Diuretics	8 (2)	170 (3)	3 (1)	39 (2)	2 (1)	42 (3)	2 (1)	14 (2)
Anticlotting and antifibrinolytic agents	7 (1)	188 (3)	1 (0)	25 (1)	12 (7)	99 (6)	2 (1)	8 (1)
Antidiabetic drugs	4 (1)	19 (0)	0 (0)	7 (0)	1 (1)	4 (0)	1 (1)	5 (1)
Psychotherapeutic agents	2 (0)	65 (1)	3 (1)	138 (8)	2 (1)	17 (1)	1 (1)	14 (2)
Antineoplastic and immunomodulating agents	2 (0)	100 (2)	1 (0)	61 (4)	1 (1)	26 (2)	0 (0)	14 (2)
Central nervous system stimulants	1 (0)	20 (0)	2 (1)	62 (4)	0 (0)	2 (0)	0 (0)	3 (0)
Contraceptives	0 (0)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	473 (100%)	5614 (100%)	360 (100%)	1697 (100%)	167 (100%)	1587 (100%)	173 (100%)	852 (100%)

*Custom classification, see online supplementary material 1.
†For all 15 different drug classes, the prevalence per 1000 persons was calculated as % of the total country-specific user prevalence (class-specific user prevalence/total user prevalence).
‡For all 15 different drug classes, the prevalence per 1000 persons was calculated as % of the total country-specific prescription prevalence (class-specific prescription prevalence/total prescription prevalence).
AUSOM, the South Korean Ajou University School of Medicine; CDARS, the Hong Kong Clinical Data Analysis and Reporting System; JMDC, the Japan Medical Data Center ; NHIRD, Taiwan's National Health Insurance Research Database; NSAID, non-steroidal anti-inflammatory drug.

Structured information on strength and formulation was used to further link drug codes to RxNorm clinical drugs (eg, 'Paracetamol 100 mg Oral Tablet'), although this more granular information was not used in this study.

Patient and public involvement

We did not involve patients or the public in our work.

Statistical analysis

Total follow-up time was calculated for each child, stratified by age group and by calendar year. Age was assessed on a day-by-day basis, and grouped according to the guidelines of the International Conference of Harmonization as <2 years, 2–11 years and 12–18 years.[14] Drugs were classified according to a custom-defined drug classification (online supplementary material 1). This classification was based on pharmacological class, and where appropriate aggregated further by indication. For each drug class, we assessed the overall user and prescription prevalence rates (per 1000 persons) per country and setting (inpatient or ambulatory) by counting the number of children using or number of dispensings of a specific drug (numerator). We used the total person count per database and per setting (inpatient or ambulatory) as the denominator to calculate prevalence rates. If a person was observed for at least 1 day in a particular category (eg, age group), that person was counted in the denominator for that category. Over the study period, and within a calendar year, children could contribute to more than one age category. For all 15 different custom drug classes the prevalence per 1000 persons was calculated as the percentage of the total country-specific user prevalence (class-specific user prevalence/total user prevalence). Lastly, we identified the five drugs with the highest user prevalence (per 1000 persons) per drug class in each country.

RESULTS

Study population

Our dynamic study cohort comprised 1 574 524 children (52.9% male). The total number of follow-up years was

Table 3 User prevalence and prescription prevalence and in an ambulatory setting by therapeutic level (prevalence per 1000 persons)

	Japan (JMDC)		Taiwan (NHIRD)		Australia (PBS)	
Class*	User prevalence (%)†	Prescription prevalence (%)‡	User prevalence (%)†	Prescription prevalence (%)‡	User prevalence (%)†	Prescription prevalence (%)‡
Antibiotics	440 (22)	882 (25)	796 (14)	2010 (8)	679 (46)	918 (52)
Corticosteroids	401 (20)	954 (27)	701 (13)	1352 (6)	348 (23)	281 (16)
Analgesics (including NSAIDs)	333 (16)	428 (12)	933 (17)	5889 (24)	96 (6)	61 (3)
Adrenergics	242 (12)	405 (11)	814 (15)	4666 (19)	184 (12)	193 (11)
Antihistamines	261 (13)	415 (12)	883 (16)	6246 (26)	3 (0)	1 (0)
Mucolytics	240 (12)	353 (10)	756 (14)	3053 (13)	0 (0)	0 (0)
Anti-infectives (excluding antibiotics and vaccines)	91 (4)	60 (2)	490 (9)	842 (3)	72 (5)	25 (1)
Contraceptives	1 (0)	1 (0)	23 (0)	17 (0)	34 (2)	27 (2)
Psychotherapeutic agents	2 (0)	7 (0)	23 (0)	41 (0)	33 (2)	86 (5)
Central nervous system stimulants	3 (0)	5 (0)	20 (0)	65 (0)	25 (2)	117 (7)
Antineoplastic and immunomodulating agents	4 (0)	7 (0)	9 (0)	15 (0)	1 (0)	3 (0)
Antiepileptics	2 (0)	5 (0)	15 (0)	44 (0)	6 (0)	41 (2)
Anticlotting and antifibrinolytic agents	3 (0)	2 (0)	13 (0)	10 (0)	1 (0)	2 (0)
Diuretics	0 (0)	1 (0)	4 (0)	5 (0)	2 (0)	2 (0)
Antidiabetic drugs	0 (0)	1 (0)	2 (0)	8 (0)	3 (0)	5 (0)
Total	2023 (100%)	3526 (100%)	5482 (100%)	24 263 (100%)	1487 (100%)	1762 (100%)

*Custom classification, see online supplementary material 1.
†For all 15 different drug classes, the prevalence per 1000 persons was calculated as % of the total country-specific user prevalence (class-specific user prevalence/total user prevalence).
‡For all 15 different drug classes, the prevalence per 1000 persons was calculated as % of the total country-specific prescription prevalence (class-specific prescription prevalence/total prescription prevalence).
JMDC, the Japan Medical Data Center ; NHIRD, Taiwan's National Health Insurance Research Database; NSAID, non-steroidal anti-inflammatory drug; PBS, the Australian Pharmaceutical Benefits Scheme .

4 783 549 years, with a mean individual follow-up of 3.0 years. The database that contributed most person years to the study was the Japanese JDMC (58 %) (table 1). Altogether, we recorded close to 9 million paediatric inpatient dispensings (8 848 699) and >44 million ambulatory dispensings (44 652 871). The relative number of dispensings prescribed per age category differed between the inpatient and ambulatory patient settings, with the highest proportion of dispensings recorded in the youngest age category (<2 years) for inpatients (45.1%) and in the middle age category (2–11 years) for ambulatory patients (67.1%).

User and prescription prevalence

The recorded user and prescription prevalence of all therapeutic agents was lower in the inpatient population than the ambulatory population (tables 2 and 3). Analgesics (including non-steroidal anti-inflammatory drugs) had the highest *user* prevalence in Korea, Hong Kong and Taiwan in the inpatient setting, however, antibiotics had the highest *prescription* prevalence in most countries (Hong Kong, Japan and Taiwan). In the ambulatory setting, antibiotics had the highest *user* prevalence in all countries, however, the highest *prescription* prevalence differed across countries. In Japan, the highest prescription prevalence was recorded for corticosteroids, while in Taiwan the highest prescription prevalence was for antihistamines and lastly, in Australia the highest prevalence was recorded for antibiotics.

Inpatient user and prescription prevalence

Overall, the inpatient user prevalence of analgesics and antibiotics was high relative to the user prevalence of other agents in all countries (table 2). Adrenergics,

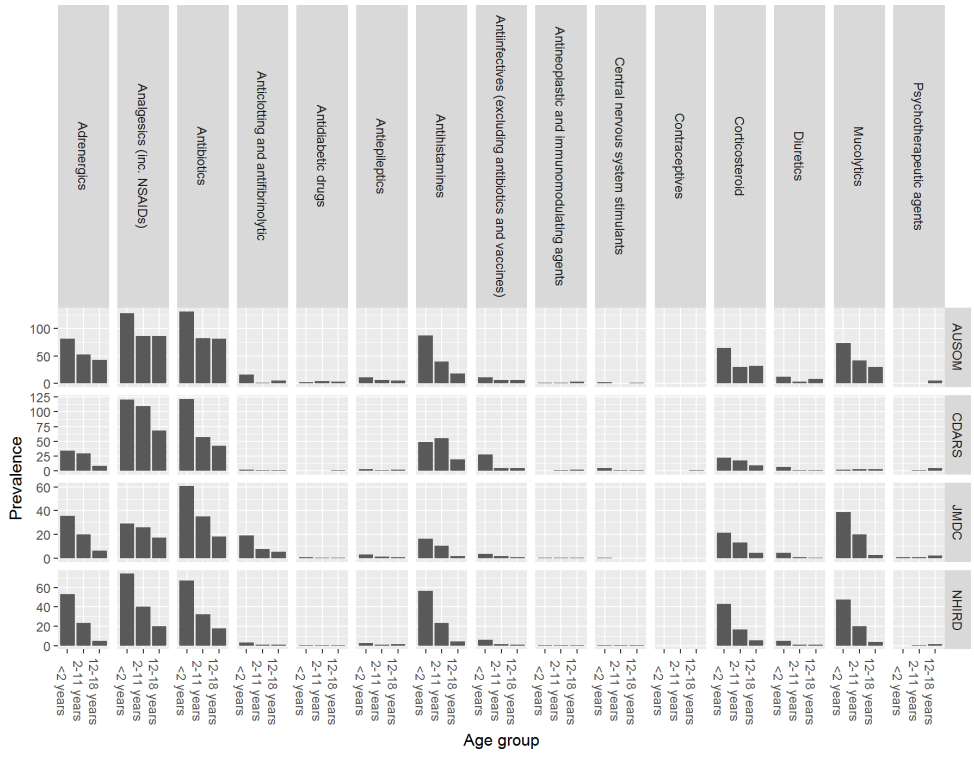

Figure 1 User prevalence by therapeutic level (prevalence per 1000 persons) and age in an inpatient setting. NSAID, non-steroidal anti-inflammatory drug.

antihistamines, mucolytics and corticosteroids were used in 10%–15% of patients while the remaining categories of medicines were used in <5% of patients. The user prevalence of mucolytics in Korea and Japan was high compared with the user prevalence of other agents. Inpatient *prescription* prevalence for different classes of agents showed patterns similar to those seen for the user prevalence.

For paediatric inpatients, overall medication use was highest in males (online supplementary material 2). The use of contraceptives, antidiabetic, psychotherapeutic, antineoplastic and immunomodulating agents was more common in females.

Results stratified by age show that the inpatient use of drugs was highest in the youngest age group (<2 years) in all but four classes (contraceptives, antidiabetic, psychotherapeutic, antineoplastic and immunomodulating agents) (figure 1).

Ambulatory user and prescription prevalence

The paediatric use of different classes of drugs in an ambulatory setting was measured in Japan, Taiwan and Australia (table 3). The highest ambulatory user prevalence across all drug classes was country specific with antibiotics ranked high in Japan (22%) and Australia (46%), followed by corticosteroids (20% and 23%, respectively). In Taiwan, the highest user prevalence of any drug class was measured for analgesics (17%), closely followed by antihistamines (16%). The pattern of inpatient *prescription* prevalence for different classes of agents was similar to the pattern seen for the user prevalence. A very low prescription prevalence of anti-infectives (not including antibiotics) was measured in all countries.

The ambulatory dispensing of drugs stratified by gender showed fewer differences between males and females in all databases (figure 2). In contrast to the gender difference seen in an inpatient setting, the ambulatory use of antibiotic agents, antihistamines and corticosteroids was higher in females.

The user prevalence by age showed a very different pattern when compared with inpatient use: the use of most drugs, by class, was highest in the middle age category (2–11 years) in Japan and Australia (online supplementary material 3). For Taiwan, the highest use for many drug classes was measured in the youngest age category. The use of contraceptives, antidiabetic, psychotherapeutic, antineoplastic and immunomodulating agents was highest in the oldest age group across all three databases.

Most commonly used drugs by class in an inpatient setting

Paracetamol was the most prevalent analgesic used in all countries, however, the prevalence of paracetamol users differed across countries with Hong Kong and Japan using mostly paracetamol while Korea and Taiwan had a greater spread of analgesic product use (table 4). Phenobarbital was the most prescribed antiepileptic agent in three countries and the second most prescribed antiepileptic agent in Taiwan. Chlorpheniramine was one of the most used antihistamines in all countries with the exception of Japan.

Differences in the most used paediatric drugs in an inpatient setting were seen for drugs with a high user

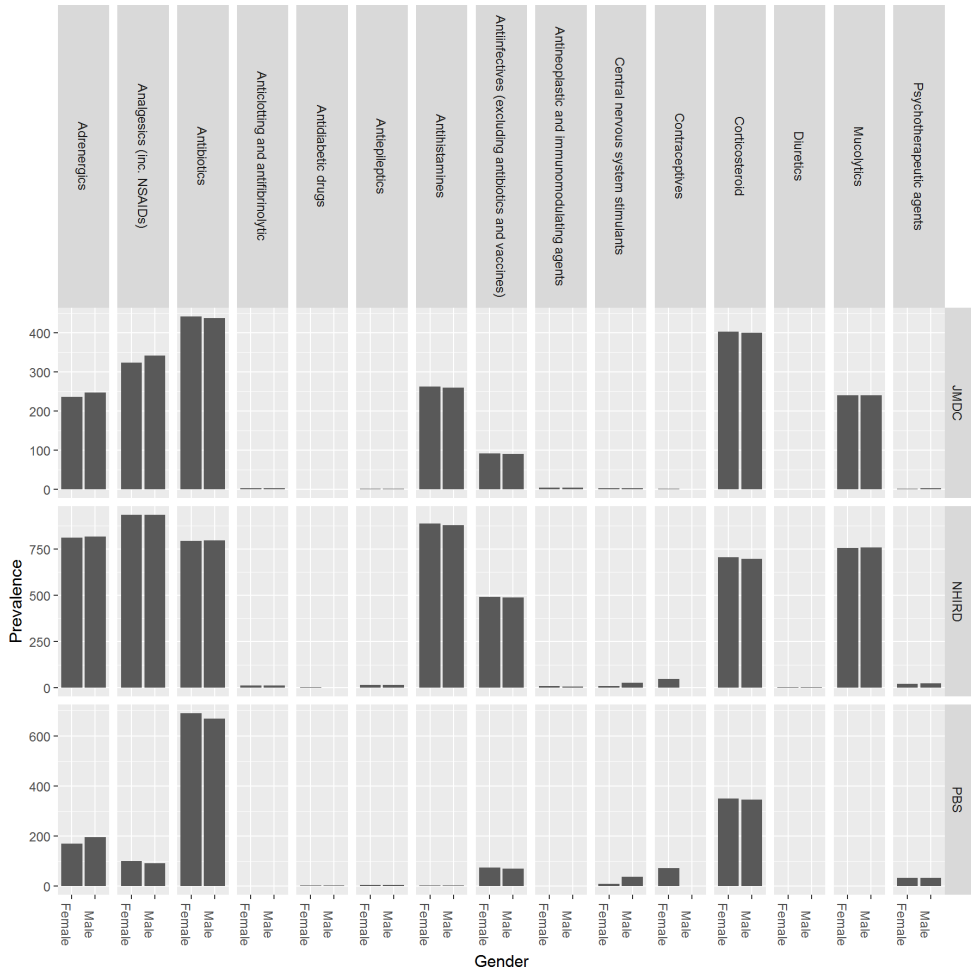

Figure 2 User prevalence by therapeutic level (prevalence per 1000 persons) and gender in an ambulatory setting. NSAID, non-steroidal anti-inflammatory drug.

prevalence overall, such as antibiotic and adrenergic agents. An outlying pattern of the user prevalence for specific agents was seen in South Korea: the most used antibiotic (ceftriaxone) and adrenergic agent (formoterol) in Korea were not among the five drugs with the highest inpatient user prevalence in any of the other East Asian countries. Furthermore, the most used mucolytic (bromhexine) and corticosteroid (dexamethasone) in Korea were less frequently used in other countries.

Most commonly used drugs by class in an ambulatory setting

As in the inpatient setting, the most used analgesic in an ambulatory setting in Japan, Taiwan and Australia was paracetamol (table 5). Overall, more similarities in the most commonly used drugs per custom-defined drug class were seen between Japan and Taiwan. For antibiotic agents, the use of amoxicillin, cephalexin and erythromycin was very similar in Taiwan and Australia. For other drug classes there was less overlap.

DISCUSSION

To our knowledge, this is the first comprehensive overview of paediatric drug use in Korea, Hong Kong, Japan, Taiwan and Australia. This study has shown a high inpatient user prevalence of analgesics and antibiotics relative to the user prevalence of other drug classes. The highest ambulatory user prevalence across all drug classes was country specific with antibiotics and corticosteroids ranked high in Japan and Australia. In Taiwan, the user prevalence of analgesics was highest followed by antihistamines. Mucolytics were among the most frequently used drugs in Korea, Japan and Taiwan, but not in Hong Kong and Australia. For paediatric inpatients, medication use was highest in males and the lowest age category (<2 years), while for outpatients gender differences were less pronounced and medication use was highest in children aged 2–11 years in Japan and Australia.

Comparison with literature

While we used a custom therapeutic classification and not ATC classification, the most commonly used drugs in every class were compared with those as reported by Sturkenboom *et al*.[3] Overall, the choice of specific paediatric therapeutic agents differed widely between the aforementioned three European countries and the East Asian countries in our study. Exceptions were similarities in the use of amoxicillin, salbutamol and paracetamol. The inpatient study results (tables 2 and 4) were compared

Table 4 Most commonly used drugs per custom-defined drug class, per country, in an inpatient setting

	Korea (AUSOM)		Hong Kong (CDARS)		Japan (JMDC)		Taiwan (NHIRD)	
Drug class	Drug name	Number per 1000 users	Drug name	Number per 1000 users	Drug name	Number per 1000 users	Drug name	Number per 1000 users
Antibiotics	Ceftriaxone	27.02	Amoxicillin	34.08	Cefazolin	10.09	Cefazolin	15.17
	Roxithromycin	19.03	Gentamicin sulfate	18.09	Ampicillin	9.2	Amoxicillin	10.9
	Cefotaxime	17.11	Penicillin G	14.33	Sulbactam	5.56	Gentamicin Sulfate	8.79
	Ofloxacin	16.84	Cefuroxime	12.72	Clarithromycin	5.25	Ampicillin	7
	Clarithromycin	10.9	Ampicillin	12.4	Cefcapene	4.61	Cephalexin	6.64
Analgesics (including NSAIDs)	Paracetamol	50.94	Paracetamol	127.67	Paracetamol	19.32	Paracetamol	30.17
	Ibuprofen	50.45	Tramadol	4.99	Remifentanil	7.34	Diclofenac	17.94
	Tramadol	28.9	Ibuprofen	4.78	Flurbiprofen	5.2	Ibuprofen	15.07
	Fentanyl	26.85	Diclofenac	1.66	Loxoprofen	4.39	Meperidine	5.21
	Ketorolac	19.11	Aspirin	1.29	Pentazocine	3.91	Ketorolac	4.81
Adrenergics	Formoterol	27.63	Salbutamol	22.81	Tulobuterol	10.32	Terbutaline	8.09
	Epinephrine	26.85	Pseudoephedrine	6.01	Procaterol	8.12	Pseudoephedrine	7.79
	Phenylephrine	14.97	Propranolol	1.02	Salbutamol	7.51	Procaterol	7.5
	Salbutamol	14.64	Terbutaline	0.97	Epinephrine	4.62	Fenoterol	4.97
	Pseudoephedrine	6.12	Phenylephrine	0.59	Ephedrine	1.8	Salbutamol	4.74
Antihistamines	Chlorpheniramine	51.7	Chlorpheniramine	38.37	Cyproheptadine	5.23	Cyproheptadine	14.26
	Ketotifen	4.02	Diphenhydramine	19.59	Epinastine	1.24	Chlorpheniramine	4.4
	Levocetirizine	1.85	Triprolidine	6.01	Ketotifen	1.12	Diphenhydramine	3.01
	Ebastine	1.23	Promethazine	2.36	Diphenhydramine	1	Brompheniramine	1.94
	Fexofenadine	1	Cetirizine	0.8	Mequitazine	0.77	Cetirizine	1.91
Mucolytics	Bromhexine	39.3	Bromhexine	2.09	Carbocysteine	18.93	Acetylcysteine	11.04
	Acetylcysteine	24.28	Acetylcysteine	1.02	Ambroxol	8.23	Ambroxol	7.18
	Mannitol	4.7	Carbocysteine	0.48	Bromhexine	4.6	Bromhexine	3.32
	Erdosteine	3.54	Mesna	0.27	Acetylcysteine	0.21	Mannitol	1.16
	Carbocysteine	0.69	–	–	Eprazinone	0.17	Carbocysteine	0.22
Corticosteroids	Dexamethasone	23.48	Prednisolone	9.34	Prednisolone	4.09	Prednisolone	4.92
	Budesonide	15.45	Hydrocortisone	7.89	Methylprednisolone	3.95	Hydrocortisone	4.61
	Prednisolone	12.11	Beclomethasone	3.6	Dexamethasone	3.36	Dexamethasone	4.4
	Hydrocortisone	10.15	Dexamethasone	2.9	Hydrocortisone	3.17	Triamcinolone	4.13
	Prednicarbate	7.74	Budesonide	1.29	Betamethasone	1.95	Methylprednisolone	3.61

Continued

Table 4 Continued

	Korea (AUSOM)		Hong Kong (CDARS)		Japan (JMDC)		Taiwan (NHIRD)	
Drug class	**Drug name**	**Number per 1000 users**	**Drug name**	**Number per 1000 users**	**Drug name**	**Number per 1000 users**	**Drug name**	**Number per 1000 users**
Anti-infectives	Oseltamivir	3.27	Hepatitis B immunoglobulin	4.35	Oseltamivir	0.5	Lysozyme	0.62
	Acyclovir	2.53	Oseltamivir	2.84	Lysozyme	0.31	Nystatin	0.54
	Fluconazole	1.3	Acyclovir	2.15	Palivizumab	0.26	Fluconazole	0.37
	Palivizumab	0.55	Clotrimazole	2.09	Acyclovir	0.24	Clotrimazole	0.29
	Itraconazole	0.49	Nystatin	1.82	Fluconazole	0.2	Acyclovir	0.24
Anticlotting and antifibrinolytic agents	Heparin	5.98	Heparin	0.91	Heparin	11.5	Heparin	1.33
	Antithrombin III	1.59	Dipyridamole	0.32	Dipyridamole	0.28	Streptokinase	0.19
	Streptokinase	0.6	Urokinase	0.27	Warfarin	0.25	Urokinase	0.11
	Urokinase	0.54	Warfarin	0.16	Antithrombin III	0.24	Dipyridamole	0.1
	Enoxaparin	0.1	Enoxaparin	0.11	Urokinase	0.07	Warfarin	0.06
Antiepileptics	Phenobarbital	3.64	Phenobarbital	1.18	Phenobarbital	0.95	Phenytoin	0.66
	Levetiracetam	2.58	Phenytoin	0.7	Carbamazepine	0.63	Phenobarbital	0.59
	Lamotrigine	2.41	Carbamazepine	0.64	Zonisamide	0.15	Clonazepam	0.51
	Topiramate	1.38	Levetiracetam	0.59	Levetiracetam	0.14	Oxcarbazepine	0.23
	Fosphenytoin	0.8	Topiramate	0.32	Clonazepam	0.14	Topiramate	0.19
Diuretics	Furosemide	6.54	Furosemide	2.41	Furosemide	1.78	Furosemide	1.58
	Spironolactone	1.32	Spironolactone	1.45	Spironolactone	0.87	Spironolactone	0.17
	Theobromine	1.2	Hydrochlorothiazide	0.43	Trichlormethiazide	0.06	Bumetanide	0.03
	Hydrochlorothiazide	0.08	–		Hydrochlorothiazide	0.02	Trichlormethiazide	0.02
	–		–		Torsemide	0.02	Amiloride	0.01
Psychotherapeutic agents	Haloperidol	0.58	Risperidone	1.34	Droperidol	0.79	Haloperidol	0.34
	Risperidone	0.52	Haloperidol	1.02	Chlorpromazine	0.37	Risperidone	0.2
	Quetiapine	0.42	Fluoxetine	0.75	Risperidone	0.26	Quetiapine	0.13
	Escitalopram	0.3	Olanzapine	0.48	olanzapine	0.11	Aripiprazole	0.09
	Fluoxetine	0.28	Sertraline	0.43	Haloperidol	0.1	Sulpiride	0.08

Continued

Table 4 Continued

Drug class	Korea (AUSOM) Drug name	Number per 1000 users	Hong Kong (CDARS) Drug name	Number per 1000 users	Japan (JMDC) Drug name	Number per 1000 users	Taiwan (NHIRD) Drug name	Number per 1000 users
Antineoplastic and immunomodulating agents	Filgrastim	0.68	Vincristine	0.43	Methotrexate	0.16	Methotrexate	0.2
	Methotrexate	0.5	Doxorubicin	0.38	Vincristine	0.14	Cytarabine	0.16
	Cyclophosphamide	0.45	Methotrexate	0.32	Cyclophosphamide	0.14	Filgrastim	0.16
	Vincristine	0.35	Cyclophosphamide	0.32	Tacrolimus	0.13	Vincristine	0.14
	Ciclosporin	0.34	Cytarabi ne	0.32	Ciclosporin	0.13	Cyclophosphamide	0.14
Central nervous system stimulants	Caffeine	0.66	Caffeine	1.4	Caffeine	0.1	Piracetam	0.27
	Methylphenidate	0.23	Methylphenidate	0.8	Atomoxetine	0.03	Methylphenidate	0.08
	Acetylcarnitine	0.05	Tomoxetine	0.11	Methylphenidate	0.02	Atomoxetine	<0.01

Drug class	Korea (AUSOM)	Hong Kong (CDARS)	Japan (JMDC)	Taiwan (NHIRD)	Drug class	Korea (AUSOM)	Hong Kong (CDARS)
Antidiabetic drugs	Regular insulin	3.24	Metformin	0.27	Regular insulin	0.5	Regular insulin	0.54
	Insulin detemir	0.32	Insulin detemir	0.11	Insulin glargine	0.06	Insulin glargine	0.09
	Insulin glargine	0.12	Gliclazide	0.11	Insulin lispro	0.04	Metformin	0.05
	Metformin	0.06	–		Metformin	0.01	Insulin detemir	0.04
	Insulin glulisine	0.05	–		Insulin glulisine	0.01	Glimepiride	0.01
Contraceptives	Megestrol	0.16	Levonorgestrel	0.16	Norethindrone	<0.01	Medroxyprogesterone	0.02
	Medroxyprogesterone	0.04	Medroxyprogesterone	0.05	Medroxyprogesterone	<0.01	Megestrol	0.01
	–		Norethindrone	0.05	–		–	

AUSOM, the South Korean Ajou University School of Medicine; CDARS, the Hong Kong Clinical Data Analysis and Reporting System; JMDC, the Japan Medical Data Center ; NHIRD, Taiwan's National Health Insurance Research Database; NSAID, non-steroidal anti-inflammatory drug.

Table 5 Most commonly used drugs per custom-defined drug class, per country, in an ambulatory setting

	Japan (JMDC)		Taiwan (NHIRD)		Australia (PBS)	
Drug class	Drug name	Number per 1000 users	Drug name	Number per 1000 users	Drug name	Number per 1000 users
Antibiotics	Clarithromycin	112.34	Amoxicillin	443.86	Amoxicillin	506.88
	Gentamicin	109.87	Cephalexin	276.72	Cephalexin	279.23
	Cefcapene	84.12	Sulfamethoxazole	217.87	Chloramphenicol	148.45
	Gentamicin sulfate	73.38	Erythromycin	170.63	Erythromycin	147.04
	Ofloxacin	72.45	Clindamycin	168.23	Cefaclor	116.35
Corticosteroids	Betamethasone	232.34	Betamethasone	353.29	Prednisolone	165.53
	Dexamethasone	154.65	Dexamethasone	285.17	Hydrocortisone	83.38
	Hydrocortisone	64.61	Triamcinolone	198.38	Fluticasone	71.28
	Prednisolone	60.3	Prednisolone	194.59	Betamethasone	65.42
	Fluorometholone	57.76	Fluorometholone	180.39	Dexamethasone	63.29
Analgesics (including NSAIDs)	Paracetamol	253.67	Paracetamol	879.68	Paracetamol	72.78
	Loxoprofen	63.76	Diclofenac	679.67	Codeine	27.87
	Salicylamide	42.91	Ibuprofen	615.18	Ibuprofen	9.71
	Dihydrocodeine	34.9	Codeine	194.02	Oxycodone	6.08
	Ketoprofen	31.47	Naproxen	101.18	Diclofenac	4.85
Antihistamines	Cyproheptadine	75.51	Dexchlorpheniramine	461.81	Cyproheptadine	3.11
	Ketotifen	57.63	Cyproheptadine	442.32	Promethazine	0.07
	Olopatadine	48.02	Cetirizine	381.81	–	–
	Clemastine	46.31	Mequitazine	338.95	–	–
	Mequitazine	35.14	Chlorpheniramine	309.08	–	–
Adrenergics	Tulobuterol	103.78	Pseudoephedrine	728.27	Salbutamol	164.14
	Epinephrine	86.05	Fenoterol	301.3	Salmeterol	32.61
	Procaterol	70.65	Procaterol	279.84	Clonidine	9.54
	Salbutamol	57.82	Tretoquinol	209.47	Epinephrine	4.15
	Phenylephrine	9.87	Terbutaline	177.29	Terbutaline	3.04
Mucolytics	Carbocysteine	175.47	Ambroxol	546.33	Dornase alfa	0.19
	Ambroxol	78.67	Bromhexine	335.46	Mannitol	0.01
	Bromhexine	49.24	Eprazinone	274.49	Acetylcysteine	0.01
	Eprazinone	8.95	Acetylcysteine	265.77	Mesna	0.01
	Acetylcysteine	8.46	Carbocysteine	197.11	–	–
Anti-infectives	Oseltamivir	41.17	Lysozyme	377.54	Nystatin	63.5
	Lysozyme	25.34	Oseltamivir	73.71	Acyclovir	1.78
	Acyclovir	14.65	Econazole	44.27	Terbinafine	1.43
	Vidarabine	6.63	Clotrimazole	29.53	Amphotericin B	1.41
	Valacyclovir	5.05	Ketoconazole	29	Ketoconazole	1.4
Psychotherapeutic agents	Risperidone	0.72	Sulpiride	7.64	Fluoxetine	9
	Sulpiride	0.37	Imipramine	3.24	Risperidone	6.59
	Imipramine	0.32	Doxepin	2.27	Sertraline	5.8
	Aripiprazole	0.32	Fluoxetine	2.12	Escitalopram	4.3
	Fluvoxamine	0.27	Risperidone	2.06	Amitriptyline	3.4
Contraceptives	Norethindrone	0.48	Norethindrone	15.18	Levonorgestrel	26.22
	Medroxyprogesterone	0.29	Medroxyprogesterone	9.53	Etonogestrel	7.82
	–	–	Lynestrenol	0.09	Medroxyprogesterone	4.81
	–	–	Megestrol	<0.01	Norethindrone	3.73
	–	–	–	–	Megestrol	0.01

Continued

Table 5 Continued

Drug class	Japan (JMDC) Drug name	Number per 1000 users	Taiwan (NHIRD) Drug name	Number per 1000 users	Australia (PBS) Drug name	Number per 1000 users
Central nervous system stimulants	Caffeine	2.11	Methylphenidate	13.54	Methylphenidate	21.24
	Methylphenidate	0.68	Piracetam	3.22	Dextroamphetamine	6.09
	Atomoxetine	0.32	Caffeine	3.2	Atomoxetine	3.28
	Modafinil	0.01	Atomoxetine	1.36	Modafinil	0.02
	Citicoline	0.01	Modafinil	0.02	–	–
Antineoplastic and immunomodulating agents	Tacrolimus	3.44	Tretinoin	6.81	Methotrexate	0.52
	Ciclosporin	0.26	Tacrolimus	0.93	Azathioprine	0.29
	Leuprolide	0.21	Methotrexate	0.38	Mercaptopurine	0.2
	Methotrexate	0.09	Azathioprine	0.29	Ciclosporin	0.16
	Vincristine	0.08	Leuprolide	0.15	Tacrolimus	0.15
Antiepileptics	Phenobarbital	1.19	Phenobarbital	9.4	Carbamazepine	2.51
	Carbamazepine	0.63	Clonazepam	2.56	Lamotrigine	1.47
	Zonisamide	0.15	Oxcarbazepine	0.99	Levetiracetam	1.18
	Clonazepam	0.15	Carbamazepine	0.99	Topiramate	1.09
	Levetiracetam	0.13	Topiramate	0.98	Phenytoin	0.41
Anticlotting and antifibrinolytic agents	Heparin	2.66	Streptokinase	9.55	Warfarin	0.42
	Dipyridamole	0.12	Dipyridamole	1.82	Enoxaparin	0.27
	Warfarin	0.11	Heparin	0.94	Clopidogrel	0.14
	Beraprost	0.04	Epoprostenol	0.16	Dipyridamole	0.02
	Ticlopidine	0.02	Warfarin	0.12	Dalteparin	0.01
Diuretics	Furosemide	0.42	Furosemide	1.78	Furosemide	0.82
	Spironolactone	0.27	Spironolactone	1.52	Spironolactone	0.51
	Trichlormethiazide	0.02	Hydrochlorothiazide	0.49	Hydrochlorothiazide	0.51
	Hydrochlorothiazide	0	Trichlormethiazide	0.4	Indapamide	0.12
	Torsemide	0	Bumetanide	0.06	Amiloride	0.03
Antidiabetic drugs	Regular insulin, human	0.09	Metformin	0.76	Metformin	1.46
	Insulin glargine	0.07	Gliclazide	0.49	Insulin glargine	0.98
	Insulin lispro	0.04	Regular insulin, human	0.36	Regular insulin, human	0.79
	Metformin	0.01	Tolbutamide	0.26	Insulin detemir	0.64
	Voglibose	0.01	Acarbose	0.25	Insulin lispro	0.22

*Custom classification, see online supplementary material 1.
JMDC, the Japan Medical Data Center; NHIRD, Taiwan's National Health Insurance Research Database; NSAID, non-steroidal anti-inflammatory drug; PBS, the Australian Pharmaceutical Benefits Scheme.

with results of a study by Rashed *et al*, who reported on the drug utilisation patterns of children admitted to a paediatric ward in the UK, Germany, Australia, Hong Kong and Malaysia.[2] As in our study, antibacterials and analgesics were the two most used therapeutic groups in all five countries.

National Korean outpatient data on paediatric polypharmacy show that in paediatric users of two or more drugs (younger than 12 years), respiratory agents are most often prescribed, followed by drugs to treat allergies, central nervous system agents and antibiotics.[5] While our study was not directly comparable as we had information on Korean inpatient dispensings only, our Taiwanese outpatient data showed a high ambulatory use of analgesics and antihistamines, while Australian and Japanese data showed a high ambulatory use of antibiotics and corticosteroids.

Implications for practice and policy: paediatric licensing of drugs in the Western Pacific region

National agencies responsible for regulating therapeutic goods often base their regulations on international guidelines, especially for new drug licensing.[15 16] For instance, in Korea it is not obligatory to carry out clinical trials for paediatrics and to develop paediatric drugs at present, while various support policies are being developed in recognition of the need for the development and provision of information on paediatric drugs (S. Cho, 2017,

personal communication). Out of the five countries included in this study, Japan is the only country with a specific paediatric working group within the Pharmaceuticals and Medical Devices Agency.[17]

Results of the current study suggest that the extent to which international paediatric prescribing guidelines affect local prescribing practices differs from country to country. For instance, our study, in line with other studies, shows the widespread of mucolytics in children in Korea, Japan and Taiwan.[6] This is a finding of note as in 2010 several European drug agencies withdrew the licences for carbocysteine and acetylcysteine for children younger than 2 years of age because their use was associated with worsening of respiratory tract infections.[18] More recently, the European Medicines Agency (EMA) published a revised assessment report on products containing ambroxol and bromhexine in which the use of these products in children below <2 years of age is discouraged.[19] Our study showed that the use of mucolytics was very high in the youngest age group in all countries but Hong Kong and Australia.

Another drug that is contraindicated for use in children in some European countries is tulobuterol. This drug, a β2-agonist, is licensed in seven countries worldwide for childhood asthma.[20 21] In 2010, the EMA refused a paediatric investigation plan for tulobuterol and granted a waiver (restricting potential use to patients>18 years) as tulobuterol was considered likely to be ineffective or unsafe in the paediatric population.[22] Yet, in this study tulobuterol was the most used adrenergic agent in an outpatient setting in Japan with 74% of all tulobuterol prescribed as patches (hokunalin tape) and the remaining 26% prescribed as a liquid (oral).

A further finding of note was the relatively common ambulatory use of dihydrocodeine in Japan and codeine in Taiwan and Australia. Both codeine and dihydrocodeine are morphine derivatives and are contraindicated for use in children younger than 12 in Europe since 2013.[23] This is mainly due to the unpredictable metabolism of codeine to morphine.[24] At the time of data collection (2009–2012), Australia already had prescribing guidelines in place in which it was recommended to restrict the use of codeine in children under 12 years.

Lastly, we found that sulfamethoxazole is still one of the most used antibiotic agents in Taiwan. In many European countries, including the UK, the importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.[25]

Strengths and limitations

We conducted the largest Western Pacific paediatric drug utilisation study to date. Data extraction was performed through a shared analysis programme and a standardised analysis process was applied to all databases. Using a CDM, and CDM vocabulary concept identifiers, we were able to use standardised drug codes across countries which allowed us to rank the user and prescription prevalence of 15 different drug classes in 5 different countries. We found some important similarities and differences in country-specific drug utilisation patterns between Korea, Hong Kong, Japan, Taiwan and Australia.

It is important to highlight that our study did not aim to directly compare the drug prevalence rates between the countries in this study, rather we aimed to provide a comprehensive overview of the country-specific pharmacological agents used in both an ambulatory and inpatient setting by gender and age. Differences in user and prescription prevalence patterns between the five countries in our study may reflect differences in the underlying prevalence of diseases, differences in physician prescribing behaviour and differences in medicine availability and data capture. Like other drug utilisation studies using EHR, we could not distinguish between these. Additionally, as medical indications were not available in all data sets we were unable to report the reasons for prescriptions. We acknowledge that this limits the clinical interpretation of our data. Formularies were different across countries as well, particularly with regard to which medicines were subsidised in the data and for which indication. It is also worth noting that we did not distinguish between formulations and we recognise that this limits the clinical interpretation of our data. Lastly, the five databases captured different source populations.

Despite the differences in databases in terms of size, setting and study populations, we believe our overview of prescription patterns and rankings is an important step to further investigate and facilitate the rational use of drugs in paediatric populations in East Asia and Australia. Standardising medication use across countries will help when implementing adverse event monitoring programmes across the region.

Over the counter (OTC) prescribing in individual countries was not captured and we may have underestimated the true drug utilisation of agents, such as paracetamol and some antihistamines. OTC prescribing is most likely to have affected any ambulatory drug utilisation estimates.

Future studies could be conducted using the current dataset in OMOP CDM format to capture any changes in paediatric drug dispensing over time. We collected data until the end of 2013 and acknowledge that, due to the rapid change in paediatric licensing of therapeutic agents, some of our findings might be worthwhile replicating with more current data.

CONCLUSION

Country-specific paediatric drug utilisation patterns were described, ranked and compared between four East Asian countries and Australia. The widespread use of mucolytics in East Asia and the use of tulobuterol in Japan warrants further investigation.

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