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Research article

Characteristics of paediatric adverse drug reaction reports in Malaysia

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ABSTRACT

During clinical trials, special populations such as children, pregnant women and elderly are excluded, creating lack of information on safety profile of medicines in these population. The lack of reliable efficacy and safety data often leads to under- or over-dosing in paediatric age groups which make them susceptible to adverse drug reactions (ADRs). This study was aimed to investigate the characteristics of ADR reports and serious ADRs among paediatric population in Malaysia. Descriptive analyses were undertaken for demographic characteristics and severity of the ADRs. Binary logistic regression was performed to identify association between selected variables and ADRs. A total of 3410 paediatric case reports for 6769 ADRs were reported within the 5-year period. Children aged one to 12 years old were the most frequently reported to experience ADRs (n=5488, 81%). Male gender exceeds more than half of the ADR reports (n=3812, 56.3%) and Malay race has the highest ADR reports (n=4780, 72%). Majority of the ADR reports were not serious (n=6285, 93%). Anti-infective medicines contributed most of the ADR reports (n=6024, 75%). The most common ADRs were from general disorders and administration site conditions (n=2879, 43%). A binary logistic regression showed male gender were more likely to experience nervous and respiratory system disorder ADRs ($p < 0.05$). Surveillance of medicines marketed for use in children must be strengthened to prevent severe life-threatening ADRs. Effective support decision tool for prescribing in paediatric population with an integrated pharmacovigilance monitoring will support continuous safety monitoring for all marketed medicines.

Keywords: Paediatrics, Adverse Drug Reactions, Adverse Drug Reaction Reporting Systems, Pharmacovigilance

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INTRODUCTION

Children are a vulnerable and high-risk population to experience ADRs due to developmental, physiological and psychological differences from the adult populations [1]. The lack of clinical studies for efficacy and safety data in children often leads to off-label prescribing and as a consequence, ADRs are unpredictable and highly prevalent [2]. A significant number of medicines are prescribed to the paediatric population on an off-label basis because they were not adequately tested and authorised for paediatric age groups [3, 4]. Only less than 15% of all marketed drugs for paediatric use have good evidence on benefit-risk balance from clinical trials [5]. The limited knowledge from clinical trials on medicines for paediatric population have made prescribing to paediatrics a challenge because children respond differently to medicines compared to adults. The lack of maturity of immune system and other rapid physiological transformation occurring in children are underlying factors which make them more susceptible to ADRs [6]. A systematic review (N=102 studies) on adverse reactions in children reported that incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children and from 0.6% to 16.8% of all children exposed to a drug during hospital stays [7]. This study found that anti-infectives and anti-epileptics were the medications frequently reported to be associated with ADRs in children admitted to hospitals whereas anti-infectives and non-steroidal anti-inflammatory drugs (NSAIDs) were frequently associated with ADRs in children in outpatient clinics. In a study conducted among children less than 5 years of age in Columbia found respiratory drugs and systemic antibiotics were the therapeutic groups mostly associated with ADRs [8]. The most affected organ system was the hematologic system in neonates, and gastrointestinal system in children less than 5 years of age. These classes of drugs were not only the most prescribed drugs for hospitalised children, but also the ones that usually cause ADRs. Meanwhile, an observational study conducted in a tertiary care hospital, India reported that most of the ADRs (60%) occurred below the age of 1 year. The major group of drugs causing

ADRs (67%) were antibiotics. The common type of ADR reported were rashes and urticaria followed by fever, anaphylactic shock, vomiting, chills, and rigors. The occurrence of ADRs increased with multiple drugs compared to single drug therapy [9].

Drug induced growth disorders as well as delayed ADRs due to maturation, growth and development of the organs have been reported in paediatrics [4]. In addition, many skin reactions (erythema, pruritis) reported in infants are related to in-utero exposure. In children (aged 2 to 11 years) attention deficit hyperactivity disorder (ADHD) medications have been reported to cause weight loss, sleep problems and decreased appetite. In teenagers (12 to 17 years), use of anti-depressants were linked to suicide ideation. Majority of the ADRs observed in paediatric prospective studies, affect the skin and subcutaneous system, gastrointestinal system, systemic reactions and reactions related to the nervous system [10]. A retrospective analysis of spontaneous ADRs among paediatric patients in Malaysia utilising spontaneous data (2000-2013) reported the most common ADRs were from the system organ classes (SOCs) of application site disorders (32.2%) followed by skin and appendages disorders (20.6%). ADRs most frequently reported were from anti-infectives for systemic use (2194/5106; 43.0%) followed by drugs from the nervous system (21.4%) and gastrointestinal system disorders (7.8%) [11]. There are limited studies among paediatric populations in Malaysia after 2015 to analyse the ADR characteristics. This study was developed to describe the five-year characteristics of ADR reporting involving Malaysian paediatric populations between the year 2016 and 2020 and also to determine the association between patient factors (age group, gender and ethnicity) and ADRs experienced by paediatric population in Malaysia.

MATERIALS AND METHODS

In Malaysia, the National Centre for Adverse Drug Reactions Monitoring serves as a database for all ADR reports and adverse events following immunisation (AEFI) reports that are submitted to the NPRA. Once reports are processed and checked for validity, viable reports were entered in the Malaysian pharmacovigilance database and sent to the World Health Organisation (WHO) collaborating centre for International Drug Monitoring and for inclusion in VigiBase in Uppsala monitoring centre. The National centre received 1245 ADR/AEFI reports in 2016 with respect to children aged less than 12 years, 1785 reports in 2017, 2687 reports in 2018 followed by 3122 reports in 2019. There is a steady increase in the number of paediatric ADR/AEFI reports received on a yearly basis [12, 13]. However, there are still limited studies among paediatric populations in Malaysia to analyse the characteristics of ADRs [11].

Data extraction

In this retrospective cohort study, data from ADR reports for neonates, infants and children aged from birth to 12 years old submitted to the National Pharmaceutical Regulatory Agency (NPRA) between 2016 to 2020 were extracted. ADR reports concerning food supplements, herbal medicines were excluded. Paediatric ADR reports collected contained information on age and gender, type of reporter, suspected drugs and ADR. In addition, medical history, investigation lab data, onset time of reaction, outcome of reaction, seriousness criteria, drug details, indication, dechallenge and rechallenge information, causal relationship between drug and ADR based on WHO – UMC causality assessment, route of administration and qualification of reporter were also extracted.

Statistical analysis

All statistical analyses were done using excel and statistical package for the social sciences (SPSS) version 26. Normality of continuous data e.g., age was checked using skewness, kurtosis and histogram. Categorical data e.g., gender was presented as frequencies and percentage. A binary logistic regression was performed to ascertain the association of age group, gender and ethnicity on the likelihood of paediatrics developing ADRs. ADRs under each SOC were studied using binary logistic regression to determine the significant associations. A p-value of < 0.05 was considered statistically significant.

Ethical Approval

This study was ethically approved by the medical research ethics committee (MREC) with NMRR ID: NMRR-20-2089-56496.

RESULTS AND DISCUSSION

Characteristics of ADRs among Malaysian paediatric population:

During the 5-year period between 2016 to 2020, there were 3410 paediatric cases comprising of 6769 ADRs involving paediatric population reported to NPRA. Table 1 shows the mean (SD) age of the paediatric patients reported to have experienced ADRs was 4.56 (3.10) years.

Table 1: Demographics of studied subjects

Demographic data	Frequency (%) N = 6769	Mean (SD)
Age (years)		4.56 (3.10)
Age group		
Neonates (birth – 1 month)	72 (1.1 %)	
Infants (1 month – 1 year)	1209 (17.9 %)	
Children (1 year – 12 years)	5488 (81.1 %)	
Gender		
Male	3812 (56.3 %)	
Female	2829 (41.8 %)	
Unknown	128 (1.9 %)	
Race		
Malay	4870 (71.9 %)	
Chinese	584 (8.6 %)	
Indian	232 (3.4 %)	
Others	1083 (16.1 %)	

SD – Standard deviation

Out of 6769 ADRs, 1.1 % (n = 72) were neonates (from birth to 1 month), 17.9% (n = 1209) were infants (1 month to 1 year) and 81.1% (n = 5488) were children (1 year to 12 years), 56.3% (n = 3812) were male and 41.8% (n = 2829) were female. This was in

contrast to a previous study conducted in Malaysia on paediatrics aged from birth until 18 years old which reported there were more females than males [11]. A multi-centre cohort study conducted in Malaysia found higher reporting rate in males similar with this study [12]. A higher trend of ADRs in males between 2 to 11 years was also observed in studies based on data from VigiBase, which acts as a repository of ADR reports for WHO-UMC [10]. In addition, in this current study, there were 71.9% (n = 4870) Malay, 8.6% (n = 584) Chinese and 3.4% (n = 232) Indian which is parallel to the race distribution in Malaysia. Also, 92.8% (n = 6285) of the reports were non-serious cases and 7.2% (n = 484) were serious cases. Among the serious cases, 1% (n = 68) were life-threatening, 5.9% (n = 396) resulted in causing hospitalisation / prolonging hospitalisation and 0.3% (n = 20) resulted in death.

Table 2: List of ADR classified by SOC according to age groups

System organ class (SOC)	Age groups			
	Children	Infants	Neonates	Total (n)
Blood and lymphatic disorders	12	4	0	16
Cardiac disorders	14	9	3	26
Ear and labyrinth disorders	5	2	0	7
Eye disorders	318	51	0	369
Gastrointestinal disorders	275	65	1	341
General disorders and administration site condition	2481	398	0	2879
Hepatobiliary disorders	2	1	0	3
Immune system disorders	12	0	0	12
Infections and infestations	43	18	0	61
Injury, poisoning and procedural complications	21	11	8	40
Investigations	45	19	3	67
Metabolism and nutrition disorders	35	8	0	43
Musculoskeletal and connective tissue disorders	22	1	0	23
Nervous system disorders	88	30	0	118
Pregnancy, puerperium and perinatal conditions	0	0	23	23
Psychiatric disorders	16	9	0	25
Renal and urinary disorders	4	4	0	8
Reproductive system and breast disorders	1	0	0	1
Respiratory, thoracic and mediastinal disorders	98	23	0	121
Skin and subcutaneous tissue disorders	1977	575	3	2555
Vascular disorders	19	10	2	31
Total	5488	1209	72	6769

Table 2 shows a big proportion of the ADRs were from general disorders and administration site conditions (42.5%, n = 2879) and skin and subcutaneous tissue disorders (37.7%, n = 2555), eye disorders (5.5%, n = 369), gastrointestinal disorders (5%, n = 341), respiratory, thoracic and mediastinal disorders (1.8%, n = 121) and nervous system disorders (1.7%, n = 118). The reported SOCs were similar to the previous findings of a paediatric study conducted in Malaysia [11]. 72% of the reported cases had onset of reaction/ADR within 24 hours after drug administration (n = 4889) which indicates the temporal relationship between drug administration and onset of reaction which is crucial for drug safety assessment [14]. Majority of the drugs reported belonged to the anatomical therapeutic chemical classification anti-infectives for systemic use category (ATC group J) (75.3 %, n = 6024) among which vaccines comprised of 55.7% (n = 4456) followed by antibiotics (19.6%, n = 1568). This was followed by drugs for the nervous system (ATC group N) which comprised of antipyretics (6.8%, n = 544) and anti-epileptics (0.6%, n = 48). Antibiotics were the major source of ADRs similar with the findings of other studies [7, 11]. Antibiotics were the major class of medications prescribed to paediatrics as a lifesaving treatment for bacterial infections. However, improper and excess use of antibiotics result in resistance, ADRs and drug toxicity. The rational use of antibiotics is essential to preserve the efficacy of available medications and to avoid ADRs [15].

Characteristics of serious ADRs

A total of 484 serious cases were reported to NPRA in between 2016-2020, out of which 383 serious ADRs were reported in children followed by eighty-one serious cases in infants and twenty serious cases in neonates.

Table 3: Serious ADR reported according to SOC and age group

System organ class (SOC)	Age groups			
	Children	Infants	Neonates	Total (n)
Blood and lymphatic disorders	8	0	0	8
Cardiac disorders	5	3	1	9
Ear and labyrinth disorders	2	1	0	3
Eye disorders	29	3	1	33
Gastrointestinal disorders	32	4	1	37
General disorders and administration site conditions	48	8	0	56
Hepatobiliary disorders	1	0	0	1
Immune system disorders	7	0	0	7
Infections and infestations	21	4	0	25
Investigations	18	9	1	28
Metabolism and nutrition disorders	4	0	0	4
Musculoskeletal and connective tissue disorders	6	1	0	7
Nervous system disorders	23	16	0	39
Pregnancy, puerperium and perinatal conditions	0	0	16	16
Psychiatric disorders	2	0	0	2
Renal and urinary disorders	0	1	0	1
Respiratory, thoracic and mediastinal disorders	27	5	0	32
Skin and subcutaneous tissue disorders	146	24	0	170
Vascular disorders	4	2	0	6
Total	383	81	20	484

Table 3 shows majority of the serious paediatric ADRs belonged to SOC skin and subcutaneous tissue disorders (n = 170) followed by SOC general disorders and administration site conditions (n = 56), nervous system disorders (n = 39), gastrointestinal disorders (n = 37), eye disorders (n = 33) and respiratory, thoracic, mediastinal disorders (n = 32). Examples of the serious ADRs reported in this study include anaphylactic reaction to NSAIDs (paracetamol and ibuprofen) and antibiotics (amoxicillin and benzyl penicillin); Stevens Johnson Syndrome (SJS) to antibiotics (amoxicillin, ampicillin and phenoxy methyl penicillin) and anti-epileptics

(carbamazepine and lamotrigine). In addition, severe neurological reactions such as oculogyric crisis were reported with the use of anti-emetic medication metoclopramide while dystonia was reported with the use of anti-psychotic medications (risperidone and prochlorperazine maleate). In response to this, NPRA issued a safety alert restricting the usage of metoclopramide in children due to serious neurological adverse events such as oculogyric crisis and dystonia. Metoclopramide package inserts were updated with contraindications in paediatrics aged less than one year and usage is restricted in paediatrics between 1-18 years old [16].

Patient demographic factors associated with ADRs

A binary logistic regression was performed to ascertain the association of age group, gender and race on the likelihood of paediatrics developing ADRs. All ADRs were classified by SOCs. ADR reports with insufficient data (e.g., unknown gender) were excluded (n = 128) leaving 6641 ADRs for regression analysis. P value < 0.05 is considered statistically significant. Table 4 shows that 14 SOCs had shown significant associations out of the reported 21 SOCs.

Table 4: Patient demographic factors associated with SOC of ADRs

SOC	N	Characteristic	B	SE	Wald	OR	95% CI OR	P-value
Blood and lymphatic disorders	15	Age group (children)	0.068	0.647	0.011	1.070	0.30-3.80	0.916
		Gender (male)	-2.314	1.036	4.992	0.099	0.01-0.75	**0.025***
		Race (malay)	1.359	0.528	6.619	**3.892**	1.38-10.95	**0.010***
Cardiac disorders	26	Age group (children)	1.005	0.451	4.972	**2.732**	1.12-6.60	**0.026***
		Gender (male)	0.038	0.442	0.007	1.038	0.43-2.47	0.932
		Race (malay)	0.076	0.484	0.025	1.079	0.41-2.78	0.875
Ear and labyrinth disorders	7	Age group (children)	0.544	0.838	0.422	1.723	0.33-8.89	0.516
		Gender (male)	-0.619	0.837	0.546	0.539	0.10-2.78	0.460
		Race (malay)	-0.820	1.081	0.576	0.440	0.05-0.66	0.448
Eye disorders	369	Age group (children)	-0.362	0.154	5.504	0.696	0.51-0.94	**0.019***
		Gender (male)	-0.107	0.109	0.957	0.898	0.72-1.11	0.328
		Race (malay)	0.172	0.117	2.185	1.188	0.94-1.49	0.139
Gastro-intestinal disorders	341	Age group (children)	0.065	0.142	0.212	1.068	0.80-1.41	0.645
		Gender (male)	0.033	0.113	0.086	1.034	0.82-1.29	0.770
		Race (malay)	0.390	0.118	10.941	1.476	1.17-1.86	**0.001***
General disorders and administration site conditions	2879	Age group (children)	-0.615	0.068	82.351	0.541	0.47-0.61	**<0.001***
		Gender (male)	0.059	0.051	1.365	1.061	0.96-1.17	0.243
		Race (malay)	-0.330	0.057	33.422	0.719	0.64-0.80	**<0.001***
Hepatobiliary disorders	3	Age group (children)	0.802	1.226	0.428	2.231	0.20-24.67	0.513
		Gender (male)	-0.337	1.226	0.076	0.714	0.06-7.89	0.783
		Race (malay)	1.676	1.226	1.869	5.342	0.48-58.99	0.172
Immune system disorders	12	Age group (children)	-14.98	1137.1	0.000	0.000	0	0.989
		Gender (male)	-0.270	0.628	0.185	0.764	0.22-2.61	0.668
		Race (malay)	0.785	0.606	1.675	2.192	0.66-7.19	0.196
Infections and infestations	61	Age group (children)	0.468	0.305	2.359	1.597	0.87-2.90	0.125
		Gender (male)	-0.689	0.303	5.173	0.502	0.27-0.90	**0.023***
		Race (malay)	1.934	0.296	42.589	**6.916**	3.86-12.36	**<0.001***
Injury poisoning procedural	40	Age group (children)	1.360	0.345	15.563	**3.894**	1.98-7.65	**<0.001***
		Gender (male)	-0.676	0.391	2.998	0.508	0.23-1.09	0.083
		Race (malay)	3.377	0.605	31.160	**29.28**	8.94-95.85	**<0.001***
Investigations	67	Age group (children)	0.819	0.271	9.167	**2.268**	1.33-3.85	**0.002***
		Gender (male)	-0.205	0.264	0.603	0.815	0.48-1.36	0.438
		Race (malay)	1.490	0.261	32.501	**4.435**	2.65-7.40	**<0.001***

N = number of ADRs reported for each SOC; a - binary logistic regression; * P-value < 0.05 considered as statistically significant.
SOC – System organ class; B – Regression coefficient; SE – Standard error; OR – Odd's ratio, CI – Confidence Interval

In this study, the male gender was found to have higher odds of developing ADRs from two SOCs; nervous system disorders (OR 1.489, 95% CI 1.027-2.159, P = 0.036) and respiratory, thoracic and mediastinal disorders (OR 1.443, 95% CI 1.006-2.068, P = 0.046). Apart from the higher prevalence of diseases such as asthma and attention deficit hyperactivity disorder among males, no definite explanation could be found [12, 17]. In addition, age group 'children' was shown to have higher odds of developing ADRs from seven out of 21 reported SOCs which were cardiac disorders (OR 2.732, 95% CI 1.129-6.609, P = 0.026), injury, poisoning and procedural complications (OR 3.894, 95% CI 1.982 – 7.652, P < 0.001), investigations (OR 2.268, 95% CI 1.335-3.855, P = 0.002), psychiatric disorders (OR 2.449, 95% CI 1.079-5.559, P = 0.032), renal and urinary disorders (OR 8.713, 95% CI 1.593-47.663, P = 0.013), skin and subcutaneous tissue disorders (OR 1.504, 95% CI 1.327-1.705, P < 0.001) and vascular disorders (OR 2.599, 95% CI 1.232-5.483, P = 0.012). Polypharmacy can be attributed to the development of higher ADRs in older children [12]. Meanwhile, Malay subjects were found to have higher odds of developing ADRs from SOC blood and lymphatic disorders (OR 3.892, 95% CI 1.382-

10.959, P = 0.010), infections and infestations (OR 6.916, 95% CI 3.869-12.362, P < 0.001), injury, poisoning and procedural complications (OR 29.285, 95% CI 8.947-95.855, P < 0.001), investigations (OR 4.435, 95% CI 2.658-7.401, P < 0.001), nervous system disorders (OR 1.992, 95% CI 1.367-2.901, P < 0.001), respiratory, thoracic and mediastinal disorders (OR 1.668, 95% CI 1.151-2.418, P = 0.007) and vascular disorders (OR 2.707, 95% CI 1.320-5.553, P = 0.007). Malay race was more likely to experience ADRs compared to other ethnicities which can be attributed to the majority of the population in Malaysia.

CONCLUSION

This study provided insight on the characteristics of ADRs experienced by the paediatric population and also revealed that during a 5-year study period, 484 serious paediatric cases were reported to NPRA. Based on logistic regression, children (1-12 years) and males' gender likely to experience ADRs. The presence of serious ADRs such as SJS, and anaphylaxis in children indicate caution is needed while prescribing antibiotics and anti-epileptics. Post-marketing surveillance of medicines for use in paediatrics is essential to identify drug-related risks among children. Active pharmacovigilance activities specific to paediatrics would reduce the exposure of paediatrics to severe or life-threatening ADRs. This study had shown active drug safety surveillance system is essential to detect drug-related ADRs among paediatric populations.

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