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Global Patterns of Adverse Drug Reactions Over a Decade

Analyses of Spontaneous Reports to VigiBase™

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Abstract

Background: Although systems to collect information about suspected adverse drug reactions (ADRs) were established in many countries and by the WHO in the 1960s, few studies have examined reported ADRs related to national income.

Objective: The aim of the study was to characterize ADRs reported to the WHO-ADR database, VigiBase™, and to relate data to national income.

Methods: We analysed ADR reports submitted to VigiBase™ from 2000 to 2009 with respect to reporting rate, age and sex of patient, type, seriousness and medications. Reports were also analysed with respect to national income level, classified in accordance with the World Bank definition: low, lower-middle, upper-middle and high.

Results: We analysed 1 359 067 ADR reports including 3 013 074 ADRs. Overall, 16% of reports were serious and 60% were reported for females. High-income countries had the highest ADR reporting rates (range 3–613 reports/million inhabitants/year) and low-income countries the lowest (range 0–21). Distribution of ADRs across income groups with respect to age group, seriousness and sex was non-significant. Overall, the majority of ADRs were reported for nervous system medications, followed by cardiovascular medicines. Low-income countries reported relatively more ADRs for anti-infectives for systemic use than high-income countries, and high-income countries reported more ADRs for antineoplastic and immunomodulating agents than lower-income groups.

Conclusion: This study showed that high-income countries had the highest ADR reporting rates and low-income countries the lowest, with large variations

across countries in each group. Significant differences in ADR reporting rates were only found for ADRs of the type 'skin and subcutaneous tissue disorders' and for the therapeutic groups 'antiinfectives for systemic use' and 'antineoplastic and immunomodulation agents'. To strengthen ADR reporting rates, especially in low-income countries, more research is needed about the impact of organizational structures and economic resources of national pharmacovigilance centres and ADR reporting practices on the large variations in ADR reporting rates within income groups.

Background

Information about the adverse drug reaction (ADR) profile of a new medicine is based on observations recorded during the clinical development process.[1] At the time of marketing, limited information about the ADR profile of the respective medicines is available, as the randomized, controlled clinical trials in which new medicines are tested do not reflect the conditions under which medicines are used postmarketing.[2,3]

The thalidomide disaster appearing in the late 1950s and early 1960s underscored the necessity of establishing national systems to monitor the safety of medicines after marketing.[4] The purpose of these systems is to acquire knowledge about drug safety problems that have not been reported prior to licensing and marketing, i.e. to identify signals of new and potentially unknown ADRs.[5,6] In 1968, the WHO established an international collaboration on medicines' safety in order to collect ADR data for individual medications at an aggregate level for as many countries as possible; in this system, all ADR reports count equally.[7] Developed countries defined as high-income countries according to the World Bank definition use more medicines; however, these countries also have greater resources in terms of money and the competency and infrastructure to survey the safety of medicines.[8] Medicine utilization, patterns and the nature of prevailing diseases, disease burden and cultural norms that may influence ADR reporting are very unevenly distributed between high- and low-income countries,[8] and the occurrence and identification of ADRs should theoretically reflect these differences. The literature provides us with extensive information about ADRs reported in high-income countries, primarily from Europe and the US,[9-12] but there is only limited information about ADRs occurring in low-income countries.[13-16] However, more information is needed about the safety of medicines postmarketing at a global level, and whether the occurrence of reported ADRs is associated with national wealth. The WHO Global Individual Case Safety Report database, VigiBase™, contains information about more than six million ADR reports from more than 100 countries. Data are reported in a standardized manner,[17] which makes the database an extremely valuable source for analysing ADR reporting patterns at a global level.

The objective of this study was to characterize globally-collected ADR reports with respect to reporting rate, age and sex, type and seriousness of ADRs, suspected medicines and national income level.

Methods

Setting

Since its establishment in the late 1960s, the WHO collaboration on drug safety has gradually expanded and 104 countries had joined the network by April 2011.[17] In 1978, the Uppsala Monitoring Centre (UMC) was established with operational responsibility for this drug safety programme, the WHO Programme for International Drug Monitoring. The primary functions of the programme are to collect, store and assess ADR reports from all member countries.[6] Countries are formally accepted as members of the WHO programme when they meet the basic requirements,

i.e. the country must have established a national ADR reporting programme, and the Ministry of Health must designate a national centre with the technical expertise to meet reporting requirements to the UMC.[6] The reports in VigiBase™ include at least one drug suspected of having caused the ADR, at least one ADR, an identification number and information on the country of origin.[11] Reports may also contain causality of the drug-ADR associations reported. Furthermore, the bulk of the information is translated into English, although free text is primarily provided in the native language.[6] Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on adverse effects from medicine use. The infrastructure of national pharmacovigilance systems varies between WHO member countries. In some countries, ADRs are reported to a national centre that stores, assesses and undertakes regulatory responses to reported ADRs. Other countries prefer decentralized systems, and the ADRs are reported to regional centres that in turn forward the reports to national centres.[6] A number of countries have made ADR reporting mandatory, while it is voluntary in many countries. ADR reporting requirements and type of reporters may differ between countries. For many years after the establishment of the first ADR reporting systems in the 1960s, only physicians were allowed to report ADRs.[18,19] However, consumers, pharmacists, and other healthcare professionals have been allowed to report ADRs over time, although not all countries have yet accepted consumer reporting in their national ADR reporting programmes.[19] Pharmaceutical companies are also required to report ADRs to the national authorities. In the majority of countries, the pharmacovigilance centres are the same as the national authorities; however, there are exceptions. The UMC has no regulatory responsibility.[6]

Data

This study included a total of 3 004 910 ADR reports reported from 96 countries added to VigiBase™ from 2000 to 2009. The following information was extracted for each ADR report: a unique report ID; date of entrance into VigiBase™; age and sex of patient, country of origin; type of reported medication, date of medication start and stop, ADR onset date, and type and seriousness of reported ADRs. ADR reports containing date of onset of an ADR before the year 2000 or reports lacking information about ADR onset were excluded. Hence, a total of 1 645 843 reports (54% of total reports) were excluded, and almost all reports without the date of onset (99%) came from countries in the high-income group.

Countries by National Income Level Per Capita

The reporting countries were divided by national income level per capita according to the World Bank's definition (definitions on income were based on US dollars, and individual calculations were made for each country according to the UN guideline): low-income group (gross national income [GNI] <$975 per inhabitant per year), lower middle-income group (GNI $976–$3855 per inhabitant per year), upper middle-income group (GNI $3856–$11 905 per inhabitant per year) and high-income group (GNI >$11 906 per inhabitant per year).[20]

Classification of Adverse Drug Reactions (ADRs) by Type

The different types of reported ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC).[21] MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Seriousness of ADRs was classified according to ICH E2A criteria.[22] Here serious ADRs are divided into the following categories: fatal, life-threatening, requiring hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity in the reporter's opinion, in a congenital anomaly/birth defect and

other medically important conditions.[22] All other ADRs are classified as non-serious.

Classification of Medications

Medicines were classified according to the Anatomical Therapeutic Chemical (ATC) Classification system.[23] The ATC system classifies medicinal products according to the primary constituent, organ or system on which they act, and their chemical, pharmacological and therapeutic properties. Medicines are divided into 14 main groups (first level), with one pharmacological/therapeutic subgroup (second level). The third and fourth levels are chemical/pharmacological/therapeutic subgroups and the fifth level is the chemical substance.[23] In this study we present data at ATC level 1.

ADR Reporting Rates

Data were analysed with regard to the following characteristics: reporting rates, ADR type and seriousness, suspected medicines and age and sex of patient. The total numbers of active ADR reports submitted are presented and a reporting rate for each country was calculated. Before an ADR report can become active in VigiBase™, it must contain information on the following four parameters: (i) country origin; (ii) report ID; (iii) type of ADR; and (iv) type of medication.[6] Reporting rate was calculated for number of ADR reports per million inhabitants per country per year using the 2008 issue of the United Nations (UN) population statistics.[24]

National datasets were not complete for the total period for all countries, as they became affiliated at different times. The patients were divided into different age groups to determine age distribution. To limit possible bias that could have been produced by differences in either the number of ADR reports or population size, the number of ADR reports within each age group was adjusted by the number of individuals within each age group. Using the same method as the UN population statistics, available data on age group statistics at national level were grouped in 5-year intervals, with patients divided into the following age groups: 0–4 years, 5–19 years, 20–44 years, 45–65 years, 65–74 years and ≥75 years. A reporting rate for these age groups was calculated for each of the reporting countries. To limit possible bias that could have been produced by differences in either the number of ADR reports or population size, the reporting rate per age group was adjusted by the number of ADR reports per million inhabitants per year divided by the number of countries within each income group. Thus, the calculated reporting rates can be considered to be for an average country within an income group.

Results

We analysed 1 359 067 ADR reports covering 3 013 074 ADRs. Approximately 85% of these reports were from high-income countries, primarily the US, UK, France, Germany, Canada and Australia. Reports from upper middle-income and lower middle-income countries constituted 7% and 8%, respectively, of all reports, and less than 1% of reports derived from low-income countries (table I). The national ADR reporting rates (reports/million inhabitants/year) varied widely among countries and income groups. High-income countries had the highest average ADR reporting rate, with 130 reports per million inhabitants per year (range 3–613), followed by upper middle-income countries with 27 reports per million inhabitants per year (range 0–261), lower middle-income countries with 12 reports per million inhabitants per year (range 0–135) and the low-income countries with 3 reports per million inhabitants per year (range 0–21).

ADRs by Age and Sex

Table II displays the distribution and ADR reporting rates by age group and national income level. No statistically significant difference was found for the distribution of ADR reports by age groups across income groups. In general, ADR reports were less frequently reported for patients in the 5–19 years age group. Large numbers of ADRs were reported for 0- to 4-year-olds and 65- to 74-year-olds in the high-income group. Across countries, approximately 60% of ADR

Table I. Countries by national income level, ranked by number of reports, year of affiliation with the WHO programme, population size, reporting rate, 2000–9

National income group[a]	Country	Year of affiliation	Population (N) by 2008[25]	ADR reports (N)	Reporting rate[b]
High-income group	US	1968	307 006 550	406 274	132
	UK	1968	61 792 000	142 555	233
	France	1986	62 610 000	111 183	174
	Germany	1968	81 735 000	95 657	116
	Canada	1968	33 739 859	67 208	201
	Australia	1968	21 955 256	64 166	302
	Italy	1975	60 187 484	37 681	65
	Spain	1984	45 929 476	36 272	90
	Sweden	1968	9 219 637	30 819	333
	Netherlands	1968	16 514 257	30 723	184
	New Zealand	1968	4 315 800	25 847	613
	Japan	1972	127 558 000	17 782	14
	Switzerland	1991	7 745 900	14 255	300
	Singapore	1993	4 978 600	13 049	280
	Norway	1971	4 828 726	10 047	216
	Ireland	1968	4 459 300	7 658	182
	Finland	1974	5 337 000	6 337	121
	Croatia	1992	4 429 078	5 278	118
	Denmark	1971	5 519 441	5 038	92
	Austria	1991	8 363 040	4 976	61
	Czech Republic	1992	10 491 492	4 929	48
	Portugal	1993	4 315 800	4 212	39
	Belgium	1977	10 666 866	3 109	30
	Slovakia	1993	5 418 374	1 768	32
	Greece	1990	11 237 068	1 734	16
	Oman	1995	10 632 482	1 202	35
	Israel	1973	7 485 600	989	14
	Hungary	1990	10 020 000	866	9
	Estonia	1998	1 340 082	231	18
	Iceland	1990	19 246	133	43
	Saudi Arabia	2009	24 807 000	86	3
	Andorra	2008	85 116	84	501
	Cyprus	2000	799 800	45	6
	Malta	2004	413 290	44	18
	Barbados	2008	274 937	21	37
	Brunei	2005	406 200	18	9
Average of high-income group		NA	NA	NA	130
Upper middle-income group	Cuba	1994	11 239 363	29 932	261
	Malaysia	1990	28 910 000	10 931	43
	Mexico	1999	107 550 697	9 573	9
	Colombia	2004	44 977 758	8 753	32

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Table I. Contd

National income group[a]	Country	Year of affiliation	Population (N) by 2008[25]	ADR reports (N)	Reporting rate[b]
	Chile	1996	16 928 873	6 313	38
	South Africa	1992	49 320 500	5 518	11
	Peru	2002	29 132 013	4 252	18
	Venezuela	1995	28 384 132	2 550	10
	Poland	1972	38 153 000	2 503	7
	Brazil	2001	194 000 000	2 250	1
	Turkey	1987	71 897 000	1 710	2
	Bulgaria	1975	7 585 000	631	9
	Macedonia	2000	2 050 671	580	28
	Serbia	2000	7 320 807	554	8
	Argentina	1994	40 134 425	528	1
	Uruguay	2001	3 344 938	463	15
	Lithuania	2005	3 339 455	285	16
	Surinam	2007	517 052	215	149
	Latvia	2002	2 254 834	212	12
	Namibia	2008	2 103 761	201	48
	Romania	1976	21 469 959	166	1
	Russia	1998	141 909 244	165	<1
	Costa Rica	1991	4 620 482	54	1
	Belarus	2006	9 665 100	44	1
	Kazakhstan	2008	15 900 000	25	1
	Botswana	2009	1 776 494	21	11
	Montenegro	2009	631 536	19	28
	Fiji	1999	837 271	1	<1
Average of upper middle-income group		NA	NA	NA	27
Lower middle-income group	Thailand	1984	66 903 277	88 784	135
	Morocco	1992	31 514 000	3 555	10
	Philippines	1995	92 150 000	3 277	3
	Iran	1998	73 920 000	2 823	4
	Tunisia	1993	10 434 500	2 593	25
	China	1998	1 331 380 000	2 433	<1
	Ukraine	2002	46 029 281	578	2
	India	1998	1 147 995 904	362	<1
	Moldova	2003	35 665 604	260	9
	Nigeria	2004	140 431 790	256	<1
	Armenia	2001	3 244 200	247	9
	Sri Lanka	2000	20 450 000	242	1
	Indonesia	1990	231 369 500	231	<1
	Jordan	2002	5 980 000	65	1
	Egypt	2001	76 822 251	19	<1
	Guatemala	2002	13 677 815	18	<1
	Sudan	2008	38 193 000	18	<1

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Table I. Contd

National income group[a]	Country	Year of affiliation	Population (N) by 2008[25]	ADR reports (N)	Reporting rate[b]
Average of lower middle-income group		NA	NA	NA	12
Low-income group	Vietnam	1999	86 024 567	2 539	3
	Ghana	2001	23 416 518	501	2
	Tanzania	1993	41 900 000	400	1
	Nepal	2006	27 504 280	322	3
	Sierra Leone	2008	4 976 871	265	21
	Madagascar	2009	18 865 000	202	10
	Ethiopia	2008	79 221 000	110	1
	Uganda	2007	30 661 300	70	1
	Zimbabwe	1998	12 260 000	57	1
	Kyrgyzstan	2003	5 128 124	48	1
	Togo	2007	5 731 000	41	2
	Senegal	2009	12 171 265	33	2
	Mozambique	2005	21 350 008	32	<1
	Uzbekistan	2006	19 810 077	29	<1
Average of low-income group		NA	NA	NA	3
Total			**1 532 674 963**	**1 359 067**	NA

a High-income group (GNI >$11 906 per inhabitant per year); upper middle-income group (GNI $3856–$11 905 per inhabitant per year); lower middle-income group (GNI $976–$3855 per inhabitant per year); low-income group (GNI <$975 per inhabitant per year).[20]

b Reports/million inhabitants/year.

ADR = adverse drug reaction; **GNI** = gross national income; **NA** = not applicable.

reports concerned females, and no significant difference was found for the distribution of sex in ADR reports across income groups.

ADRs by Type and Seriousness

Table III displays the distribution of reported ADRs by SOC and national income. The majority of ADRs were reported for the SOCs 'general disorders and administration site conditions' (15% of total ADRs), 'skin and subcutaneous tissue disorders' (14% of total ADRs) and 'nervous system disorders' (12% of total ADRs). For the SOC 'skin and subcutaneous tissue disorders', we found a difference in the distribution by income group as the lower-income groups reported more skin reactions than high-income countries (Chi-squared = 36.56; $p < 0.01$). For all countries, 16% of all reported ADRs were serious, but no statistically significant differences in the distribution of serious ADRs were found across income groups (data not reported in this study).

ADRs by Therapeutic Groups

Table IV displays the distribution of reported ADRs by therapeutic group. Overall, the majority of ADRs were reported for 'nervous system' medications (ATC group N) [16% of total ADRs], followed by 'cardiovascular system' medications (ATC group C) [13% of total ADRs], while a large number of ADRs were reported for medications without an ATC code [12% of total ADRs]. It was predominantly the high-income countries that reported ADRs for the 'cardiovascular system' (ATC group C) and 'nervous system' (ATC group N) medications. For the therapeutic groups 'antiinfectives for systemic use' (ATC group J) [Chi-squared = 19.6; $p < 0.01$] and 'antineoplastic and immunomodulating agents' (ATC group L) [Chi-squared = 13.2; $p < 0.01$], we found a difference in the distribution by income groups. Lower middle- and low-income countries reported more ADRs for medications from ATC group J than high-income countries, and high-income countries

reported more ADRs for medications from ATC group L than the other countries.

Discussion

This is the first study that has analysed general ADR reporting patterns on a global level related to national income level. Our analyses showed that high-income countries had the highest ADR reporting rates and low-income countries the lowest, with large variations observed across countries. Significant differences in ADR categories across countries and income level were only found for ADRs of the type 'skin and subcutaneous tissue disorders' and for the therapeutic groups 'antiinfectives for systemic use' (ATC group J) and 'antineoplastic and immunomodulating agents' (ATC group L).

ADR Reporting Rates

The high-income countries submitted the largest number of ADR reports to VigiBase™; this reporting pattern was expected since the majority of the high-income countries have long-term and well established pharmacovigilance systems.[7] A study analysing ADRs reported to VigiBase™ for antimalarial medications also demonstrated higher reporting rates from high-income countries than from low-income countries.[25] There were wide variations in reporting rates within country income level and we suspect that organizational structures and resources of national pharmacovigilance systems are a major explanatory factor. Some countries forward only selected cases to WHO rather than all ADR reports, e.g. because of limited resources for translating national reports into English. Therefore, the actual national reporting rates are probably higher than found in the WHO database. Many new signals are applicable cross-nationally, and differences in overall reporting rates may in some instances have a large impact. Examples are the many serious cases of haemolytic anaemia that occurred after the use of intravenous artesunate for treating severe malaria in Europe.[26] Prior to marketing, few of these serious cases had been reported for artesunate in the clinical developments trials conducted in Norway.[26] This example stresses the need to improve the surveillance in specific subsets of populations such as children, or specific countries such as West African countries.[6]

ADRs by Age

In general, because the elderly use more medicine than younger people, this patient group is at greater risk of experiencing more ADRs, and we expected the majority of reports to concern people above 65 years of age. However, our analysis showed that this assumption was confirmed only for the high-income group. No major differences in ADR distribution were observed among age groups in the lower-income groups. Due to major differences in the general population distribution with respect to age between high- and low-income countries, we would have expected a larger share of reports regarding children and adolescents in the lower-income groups than reported. We have no explanation for these reporting patterns.

Table II. Distribution of adverse drug reaction reports (number and average reporting rates) by age groups and national income level, 2000–9

National income level[a]	Age group (y)					
	0–4 [N (%)][b]	5–19 [N (%)][b]	20–44 [N (%)][b]	45–64 [N (%)][b]	65–74 [N (%)][b]	≥75 [N (%)][b]
High-income group	205 (24)	64 (8)	79 (9)	136 (16)	211 (25)	144 (17)
Upper middle-income group	29 (16)	10 (5)	28 (15)	43 (23)	45 (25)	29 (16)
Lower middle-income group	14 (16)	5 (6)	11 (13)	17 (20)	23 (26)	17 (19)
Low-income group	4 (16)	3 (11)	3 (12)	5 (18)	4 (15)	8 (29)

a High-income group (GNI >$11 906 per inhabitant per year); upper middle-income group (GNI $3856–$11 905 per inhabitant per year); lower middle-income group (GNI $976–$3855 per inhabitant per year); low-income group (GNI <$975 per inhabitant per year).[20]

b N = ADR reports/million inhabitants/year.

ADR = adverse drug reactions; **GNI** = gross national income.

Table III. Reported adverse drug reactions by system organ class and national income level, 2000–9

System Organ Class[a]	National income group (total [N])[b]				
	High (2 686 460)	Upper-middle (153 444)	Lower-middle (164 536)	Low (8634)	Total ADRs (3 013 074)
General disorders and administration site conditions	16	11	9	14	15
Skin and subcutaneous tissue disorders	11	24	57	43	14
Nervous system disorders	12	14	5	9	12
Gastrointestinal disorders	11	18	11	11	11
Investigations	5	2	1	1	5
Psychiatric disorders	6	3	1	1	5
Respiratory, thoracic and mediastinal disorders	5	5	5	4	5
Cardiac disorders	4	3	2	2	4
Musculoskeletal and connective tissue disorders	5	2	1	1	4
Blood and lymphatic disorders	3	3	1	1	3
Infections and infestations	4	1	0	1	3
Vascular disorders	3	4	1	2	3
Eye disorders	2	2	2	1	2
Injury, poisoning and procedural complications	3	0	0	0	2
Metabolism and nutrition disorders	2	2	1	1	2
Renal and urinary disorders	2	1	0	1	2
Ear and labyrinth disorders	1	1	1	2	1
Hepatobiliary disorders	1	1	1	1	1
Immune system disorders	1	1	2	4	1
Neoplasms benign, malignant and unspecified	1	0	0	0	1
Reproductive system and breast disorders	1	1	0	1	1
Total	**100**	**100**	**100**	**100**	**100**

a Values are expressed as a percentage of the total.

b High-income group (GNI >$11 906 per inhabitant per year); upper middle-income group (GNI $3856–$11 905 per inhabitant per year); lower middle-income group (GNI $976–$3855 per inhabitant per year); low-income group (GNI <$975 per inhabitant per year).[20]

ADRs = adverse drug reactions; **GNI** = gross national income.

ADRs by Type and Seriousness

No differences were detected in the distribution of serious and non-serious ADRs across country income groups, despite differences in medicine use patterns between high- and low-income countries and differences in access to ADR reporting facilities.[8,27] In theory, at least, there should be differences, as different medicines are used across countries and geographic regions.[8] ADR reporting patterns were also in accordance with previous studies.[9-13] The lower-income groups reported more ADRs of the type 'skin and subcutaneous tissue disorders'. Serious ADRs such as erythema multiforme, purpura and Stevens-Johnson syndrome were reported from the use of 'antivirals for systemic use' (ATC group J05) in African countries. This may be explained by the fact that African countries belong to this income group and skin reactions occur more frequently in this population.

ADRs by Therapeutic Group

'Antiinfectives for systemic use' (ATC group J) was the only therapeutic group for which significant differences were found across regions, with a higher prevalence of ADRs reported for these medications in Africa, Central America and Eastern Asia. This finding could be explained by the fact that these medications are used to treat diseases such as HIV/AIDS, malaria and tuberculosis, which have a higher prevalence in low-income countries, particularly in Africa and Eastern Asia.[28] For 'antineoplastic and immunomodulating

agents' (ATC group L), the highest number of ADRs was reported in high-income countries, where patients have greater access to this type of medication than patients in low-income countries.[29]

Strengths and Limitations

The main purpose of the spontaneous reporting systems is to identify rare and serious ADRs that appear after the medications are marketed. However, spontaneous reporting systems have well known limitations, i.e. underreporting, report quality and the fact that spontaneous ADR reports cannot be used to determine incidence or prevalence of ADRs since the denominator of medicine usage is unknown. However, despite these well known limitations, the spontaneous reporting system remains a cornerstone in the surveillance of new ADRs. The major strengths of this global study are the use of VigiBase™ covering many countries over a longer period of time and the very large sample of ADRs. However, the diversity in reporting rates across low- and high-income countries and the differences in the length of the countries' affiliation with the WHO programme make interpretations very difficult. The data do not offer an explanation as to whether different reporting patterns are related to the differences in the structures and cultures of national ADR reporting programmes, differences in medicine utilization patterns and/or differences in disease patterns. To analyse this large dataset, we aggregated data at SOC level 1, therapeutic group (ATC level) and income level, which may have resulted in lack of significant results between income groups. If ADR reporting patterns had been analysed at lower levels of the SOC and ATC systems as well as at country level, more

Table IV. Reported adverse drug reactions by therapeutic group (Anatomical Therapeutic Chemical level 1) and national income level, 2000–9

ATC group (level 1)[a]	National income group (ADRs [N])[b]				
	High (3 780 368)	Upper-middle (205 169)	Lower-middle (362 164)	Low (10 733)	Total (4 358 434)[c]
Alimentary tract and metabolism (A)	11	9	8	8	11
Blood and blood forming organs (B)	5	3	2	2	4
Cardiovascular system (C)	14	13	8	4	13
Dermatologicals (D)	4	5	5	6	4
Genito-urinary system and sex hormones (G)	3	3	4	2	3
Systemic hormonal preparations, excluding sex hormones and insulins (H)	3	2	1	1	3
Antiinfectives for systemic use (J)	5	14	19	31	7
Antineoplastic and immunomodulating agents (L)	9	4	1	1	8
Musculo-skeletal system (M)	6	8	11	4	7
Nervous system (N)	16	13	11	7	16
Antiparasitic products, insecticides and repellents (P)	<1	1	1	5	1
Respiratory system (R)	5	4	6	2	5
Sensory organs (S)	5	12	13	15	6
Various (V)	1	1	1	1	1
Medications without ATC code	12	9	10	13	12
Total	**100**	**100**	**100**	**100**	**100**

a Values are expressed as a percentage of the total.

b High-income group (GNI >$11 906 per inhabitant per year); upper middle-income group (GNI $3856–$11 905 per inhabitant per year); lower middle-income group (GNI $976–$3855 per inhabitant per year); low-income group (GNI <$975 per inhabitant per year).[20]

c Number of ADRs higher than the total number, because ADRs that appeared in reports contained more than one reported medication or an ADR counted once for every possible combination between a medicine and an ADR.

ADRs = adverse drug reactions; **ATC** = Anatomical Therapeutic Chemical; **GNI** = gross national income.

detailed information about type of reported ADRs and medications could have been provided. Missing data due to delay in reporting from various national pharmacovigilance centres to the UMC is likely to have affected the results. Particularly for the years 2007–9, it is reasonable to assume that not all ADR reports were submitted before 31 December 2009, which was the closing date for our dataset. As a consequence, the number of ADR reports submitted for recent years is likely to be underestimated compared with the earlier years in the decade. Reporting rate and age were based on the latest available UN population statistics and, therefore, the ADR reporting rates could be underestimated, especially for the countries with the fastest growing populations, but it is unclear whether comparisons across countries are influenced by these limitations. Patients reporting ADRs were divided into age groups according to the UN population statistics, but we do not consider this issue to have affected the overall results of this study. A large number of ADR reports were excluded due to a lack of date of onset of the reported ADRs, the vast majority from the high-income group, in these six countries in particular: Australia, Canada, Germany, the Netherlands, UK and the US. These countries submit the majority of reports to VigiBase™ and the exclusion of reports without an ADR onset date from these countries is less likely to influence the overall results of this study. If we had included all ADR reports from VigiBase™ without an ADR onset date, it could have provided a biased picture of ADR patterns.

Conclusions

This study showed that high-income countries had the highest ADR reporting rates and low-income countries the lowest, with large variations across countries in each group. Significant differences in ADR reporting rates were only found for ADRs of the type 'skin and subcutaneous tissue disorders' and for the therapeutic groups 'antiinfectives for systemic use' and 'antineoplastic and immunomodulation agents'. More research is needed about the impact of organizational structures and economic resources of national pharmacovigilance centres and ADR reporting practices to gain insight into the large variations in ADR reporting rates within income groups in order to strengthen ADR reporting rates, especially in low-income countries.

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