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Global Reporting Patterns of Suspected Adverse Drug Reactions and Their Relationship with a Country's Socioeconomic Status- Insights from VigiBase Data

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Abstract:
Introduction: Individual Case Safety Report (ICSR) reporting rates remain low in low- and middle-income countries, largely due to weak pharmacovigilance systems. While the influence of income on reporting rates has been previously studied, the roles of health and education, along with the combined effect of these key country-level indicators, have not been examined globally.
Aims: To compare global ICSR reporting patterns and quantify potential differences in their characteristics across pre-defined socioeconomic strata of countries.
Methods: This observational descriptive quantitative study analyzed ICSRs from VigiBase for members of the World Health Organization Programme for International Drug Monitoring, from 01/01/2010 to 31/12/2022. Yearly population data and Inequality-adjusted Human Development Index (IHDI) values were sourced from the United Nations Development Programme (UNDP). Yearly reporting rates for each full member country were calculated, and their medians were computed over the study period. The median IHDI and its components (Health, Education, and Income) were determined for each country and categorized into four human development groups: low, medium, high, and very high. To examine the relationship between IHDI, its components, and reporting rates, a linear regression model was used. vigiPoint was employed to compare the relative frequency of covariates in ICSRs from countries with low, medium, and high IHDI, with those from very high IHDI countries. Scatter plots were used to explore the relationship between ICSR reporting rates and IHDI.
Results: Regression analysis showed a significant positive relationship between case report rates and IHDI and its components (R^2 = 0.402–0.457). Low IHDI countries had more physician and pharmacist reports, while very high IHDI countries had more consumer submissions and clinical study reports but lower report completeness. Drug types and adverse events (AEs) varied by IHDI level, with lower IHDI countries focusing on infectious disease treatments and higher IHDI countries on immunosuppressants and opioids. Reported AEs also differed, with vomiting and pyrexia being more common in low IHDI regions, and drug ineffectiveness and fatigue more common in very high IHDI regions.
Conclusion: This study shows that human development, as measured by IHDI, plays a key role in ICSR reporting rates. Improving human development factors could help strengthen pharmacovigilance, especially in low and medium IHDI countries.

1 INTRODUCTION

An adverse drug reaction (ADR) is defined as a harmful or unpleasant reaction because of an intervention related to the use of a medicinal product. It not only predicts hazard from future administration but also warrants prevention or specific treatment, or alternatively, an alteration of the dosage regimen, or even withdrawal of the product (Edwards & Aronson, 2000). ADRs pose a significant public health burden, contributing to a median of 5.5% of hospitalizations in developing countries (IQR: 1.1–16.9%) and 6.3% in developed countries (IQR: 3.3–11.0%). Mortality rates due to ADRs are similarly concerning, with medians of 1.8% (IQR: 0.8–8.0%) in developing countries and 1.7% (IQR: 0.7–4.8%) in developed countries (Angamo et al., 2016). Besides increasing morbidity and mortality, ADRs often lead to prolonged hospital stays and place considerable strain on healthcare systems (Sultana et al., 2013). Pre-approval studies, including randomized controlled trials, are fundamental for evaluating a drug's safety and efficacy before it reaches the market. However, they are not designed to detect rare or delayed ADRs. The statistical power of most clinical trials is insufficient to identify rare ADRs; even in the absence of observed adverse events (AEs), reactions with low incidence may still be present (Onakpoya, 2018). In addition, the limited follow-up duration of these studies often fails to capture long-latency ADRs. Since ADRs are typically not primary endpoints in Phase III trials, they are often under-assessed (Naranjo et al., 1982), and reporting remains inconsistent (Loke & Derry, 2001), despite some efforts to improve transparency (Page et al., 2021).

Rare ADRs, among others, are typically detected throughout the life cycle of a drug (Aronson, 2023), as part of pharmacovigilance, that is: "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems" (World Health Organization, 2002). Information regarding ADRs may derive from Individual Case Safety Reports (ICSRs). ICSR refers to the format and

content for reporting one or several suspected ADRs concerning a medicinal product that occurs in a single patient at a specific time (European Medicine Agency, 2014). The systematic collection and analysis of ICSRs in databases has historic roots in the wake of the "thalidomide tragedy" of 1961 (van Grootheest, 2003). The WHO (World Health Organization) Programme for International Drug Monitoring (PIDM) began in 1968, and a decade later, the Uppsala Monitoring Centre (UMC) was founded to handle its operational functions. UMC was designated as a WHO Collaborating Centre for International Drug Monitoring to serve as a global hub for detecting and monitoring ADRs. To date, UMC manages VigiBase, the WHO global database of adverse event reports for medicines and vaccines, collecting ICSRs from members of the WHO PIDM. The WHO PIDM has two types of member countries: full members and associate members. Full members of the WHO PIDM are national centers that have completed the application process and met all reporting requirements, allowing them to fully engage in the pharmacovigilance network. Associate members are those whose applications have been accepted but are still in a transitional phase, receiving support from WHO and UMC while working towards full membership by submitting ICSRs and ensuring compliance with reporting standards (Uppsala Monitoring Centre, n.d.). However, in low- and middle-income countries, ADRs often go underreported, largely due to weak regulatory enforcement and limited awareness about pharmacovigilance (Kiguba et al., 2023).

Up-to date, only one study has examined the relationship between ADR reporting patterns in VigiBase and national income levels, as defined by the World Bank (Aagaard et al., 2012). In contrast, the Human Development Index (HDI), a broader socioeconomic measure developed by the United Nations Development Programme (UNDP) to reflect a country's overall well-being and human capabilities, has not yet been explored in relation to ADR reporting patterns. The HDI summarizes a country's achievements in three dimensions of human development: life expectancy at birth, expected and mean years of schooling, and GNI per capita (UNDP, 2024a) . An observational descriptive quantitative study conducted in ASEAN countries found a correlation between HDI and economic growth (Elistia & Syahzuni, 2018). However, the same does not hold for all countries (Pekarčíková &

Prachařová, 2023). For instance, countries with high Gross National Income (GNI) per capita may still have low HDI. A notable example is Switzerland, which ranks 1st in the UNDP Human Development rankings with a GNI per capita of $69,433, while Qatar, with a GNI per capita of $95,944, ranks 40th (UNDP, 2024b). While the HDI seems useful broader socioeconomic index, it does not account for inequality within countries. To overcome the limitation of HDI, this study focuses on a more nuanced metric of human development, the Inequality-adjusted Human Development Index (IHDI), that accounts for inequalities in life expectancy, education, and income within a country (UNDP, 2024a). The study aims to explore country-level correlations between the IHDI and its dimensional indices with reporting rates of ADRs, as well as to investigate differences in the characteristics of these reports across various IHDI groupings.

2 METHOD

2.1 Data Sources

2.1.1 VigiBase

In this observational descriptive quantitative study, ICSRs submitted to VigiBase, the WHO global database of reported adverse events of medicinal products, by full member countries of the WHO PIDM were studied. Numbers of deduplicated ICSRs were retrieved for each country from VigiBase, irrespective of the involvement of a medicinal product in the ICSR (suspected, interacting, or concomitant). AEs in VigiBase are coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), while the associated medicinal products are classified using WHODrug Global.

2.1.2 UNDP Human Development Reports Data Center

IHDI values, along with the corresponding values for its three dimensions and population data for the study period were available at the UNDP Human Development Report DataCenter; however, the dimensional indices were not provided. These indices were separately calculated using data and tools provided by the UNDP, following the methodologies outlined in their technical notes (UNDP, 2024a).

2.2 Calculation of HDI and IHDI

To calculate the HDI, dimension indices for health, education, and income were created using predefined minimum and maximum values and then normalized on a scale from 0 to 1. The GNI per capita was transformed using its natural logarithm. The overall HDI was calculated as the geometric mean of the three-dimension indices (UNDP, 2024a).

The IHDI accounts for inequality in the distribution of the three dimensions across the population, using the Atkinson inequality measure (Ax) (UNDP, 2024a). This compares the geometric (g) and arithmetic (μ) means of each dimension's distribution. For mean years of schooling, Ax defaults to one year to avoid zero values. The dimensional indices were adjusted for inequality by multiplying the original HDI indices (Ix) by 1 - Ax. The geometric mean of these adjusted indices gives the IHDI:

*IHDI= [(1-AHealth). (1-AEducation). (1-AIncome)] 1/3*HDI*
Where, A= Calculated inequality in respective distributions

As for the HDI, IHDI values range from 0 to 1 (United Nations Development Programme,2023).

2.3 Inclusion and exclusion criteria

This study included ICSRs submitted to VigiBase by full members of the WHO PID between the 1st of January 2010 and the 31st of December 2022. ICSR submissions outside this timeframe were excluded since the IHDI was introduced in 2010, with the most recent data available through 2022. Additionally, ICSRs related to COVID-19 vaccines were excluded, to minimize the impact of the large influx of ICSRs on reporting patterns resulting from the SARS-CoV-2 pandemic. ICSRs from countries that were no longer members of the WHO PIDM were excluded, and so were those countries lacking IHDI values for the entire study period since IHDI was a key variable in this study. Duplicates were excluded using vigiMatch, a duplicate detection algorithm (Norén et al., 2005).

2.4 Categorization of countries

The countries in this study were classified into four human development groups based on their median IHDI values over the study period, following the UNDP classification. The groups were defined as: very high (IHDI above 0.800), high (IHDI between 0.700 and 0.799), medium (IHDI between 0.550 and 0.699), and low (IHDI below 0.550).

2.5 Data analysis

2.5.1 Descriptive statistics

To explore how overall human development with inequality adjustment may influence a country's reporting rate, annual ICSR reporting rates for each country were calculated by dividing the total number of ICSRs submitted per year by that year’s population. From these annual rates, a median reporting rate was calculated for each country across the entire study period. Similarly, the median IHDI and dimensional indices for each country were derived over the study period.

2.5.2 Data Presentation

To visualize the relationship between ICSR reporting rates and IHDI (along with its dimensional indices), scatter plots were generated.

2.5.3 Statistical Analysis

To evaluate the relationship between the independent variables (IHDI and its dimensions) and the dependent variable (ADR reporting rate), linear regression models were conducted separately for each independent factor. This approach was necessary due to the high correlation among the independent variables, as confirmed by testing with the Variance Inflation Factor (VIF) (see appendix 1). All statistical analysis and visualizations were performed using Python 3.12.4.

2.5.4 vigiPoint Comparison

To compare the characteristics of ICSRs across countries, the analysis used vigiPoint, which is a data exploration tool in pharmacovigilance that identifies associations between subjects of interest and key covariates in ADR reports available in VigiBase. Associations were quantified using shrunken log odds ratios (SLORs), derived from posterior distributions to account for data variability and sparsity. The strength of association was measured using the vigiPoint score, defined as the absolute value of the lower bound of the 99 % credibility interval for the SLOR, or the upper bound in the case of negative associations. Covariates with vigiPoint scores exceeding the predefined threshold (T = 0.5) were considered to show strong and statistically significant associations (Wakao et al., 2019). To facilitate interpretation, odds ratios were presented in result section, as they provide an intuitive measure of the strength and direction of associations.

In this study, the subsets of interest were low, medium, and high IHDI groups and the comparator one was the subset of countries whose IHDI was very high. The covariates of interest for analysis were age group; completeness (a metric that quantifies the technical completeness of ICSRs ((Bergvall et al., 2014)); reported fatality; notifier; patient sex; report type; seriousness; group of reported drugs according to ATC third level (SpATClvl3); and events coded to preferred terms (MedDRAPT). For seriousness classification, a ICSR was classified serious if it meets one or more of the following criteria: results in death, is life-threatening, requires or prolongs hospitalization, leads to persistent or significant disability/incapacity, causes a congenital anomaly/birth defect, or is deemed medically important by a healthcare professional (ICH Expert Working Group, 2001).

3 RESULTS

3.1 Descriptive statistics

The results present the annual ICSR reporting rates for each country, along with the median reporting rates, IHDI scores, and their dimensional indices over the study period, which are provided in Annex 1. Scatter plots illustrate the relationships between median ICSR reporting rates (log transformed) and the median IHDI, along with its three component indices—income, life expectancy, and education (Figure 1). All four plots showed a positive association, indicating that countries with higher IHDI and dimensional scores tend to report more ADRs.

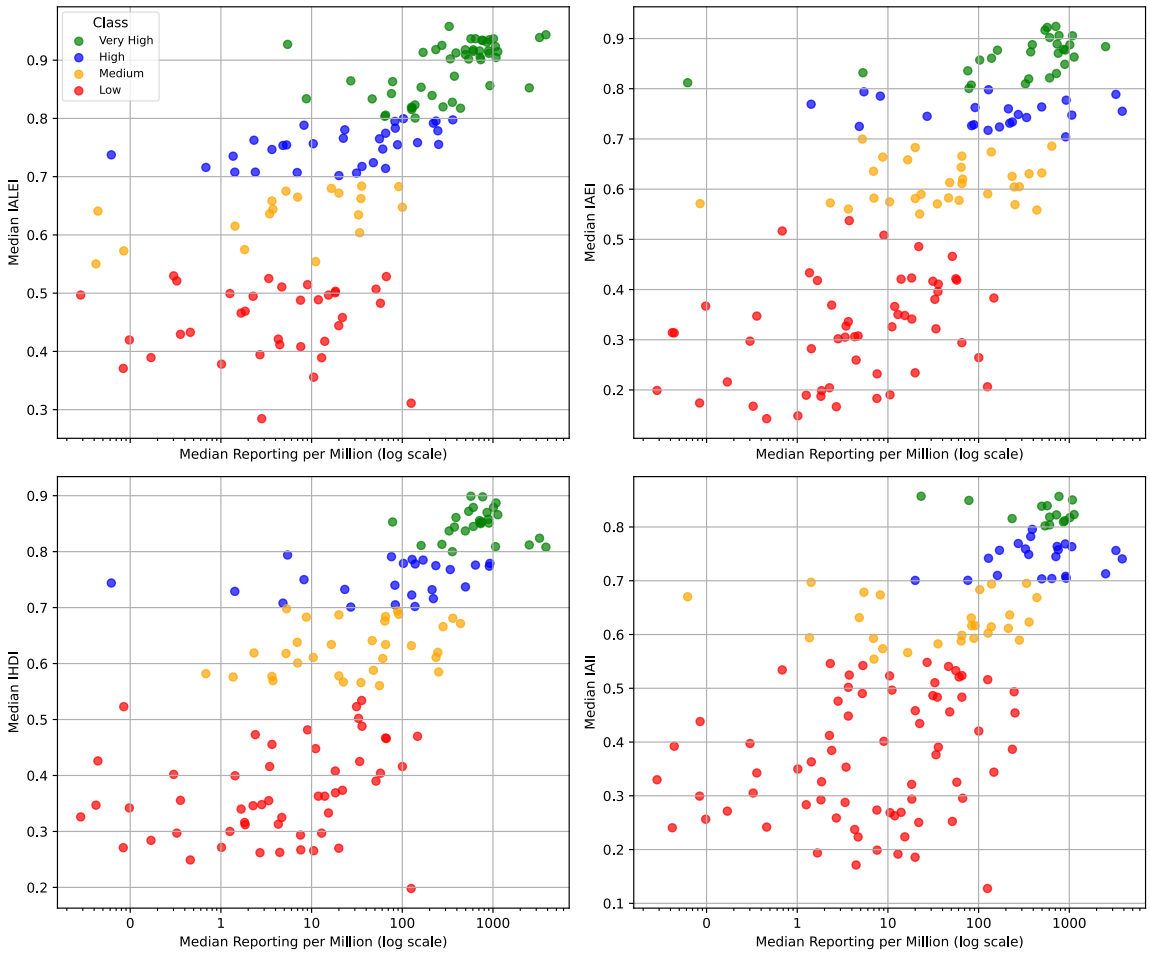

Figure 1. Scatter plots showing the association between ICSR reporting rates per country and the IHDI and its components. IHDI refers to the Inequality-adjusted Human Development Index; IALEI to the Inequality-adjusted Life Expectancy Index; IAII to the Inequality-adjusted Income Index; and IAEI to the Inequality-adjusted Education Index. The Median IHDI, Median IALEI, Median IAII, and Median IAEI values represent the median of each respective index calculated for each country over the study period. The colour code corresponds to the Y-axis values (see Method Section 2.4 for details).

3.2 Statistical analysis

The regression analysis showed a significant positive relationship between the reporting rate of case reports and the IHDI, as well as its three-dimensional indices: health, education, and income. The coefficients for median IHDI value, median IALEI (Inequality Adjusted Life Expectancy Index) value, median IAII (Inequality Adjusted Income Index) value, and median IAEI (Inequality Adjusted Education Index) value indicated strong positive associations, with

R-squared values ranging from 0.402 to 0.457, suggesting a meaningful explanatory power of these variables (Table 1).

Table 1. Regression results for the relationship between reporting rate of case reports and IHDI and its dimensional indices.

Independent variables	Coefficient(β)	Std. Error	t-value	p-value	R-squared
median_IHDI_value	9.48	0.87	10.94	<0.0001	0.46
median_IALEI_value	10.06	0.98	10.23	< 0.0001	0.42
median_IAII_value	9.03	0.93	9.77	< 0.0001	0.40
median_IAEI_value	7.99	0.76	10.51	< 0.0001	0.44

3.3 vigiPoint comparison

Countries in the very high IHDI group reported higher cases without patient age information compared to low, medium, and high IHDI groups (36.4% vs. 9.26%, 4.12%, and 14.95%, respectively). Additionally, in the very high IHDI group, a larger percentage of reports were missing information about the patient's sex compared to the other groups (7.79% vs. 3.28%, 1.13%, and 4.67%) (Table 2).

Table 2. Comparison of age and sex distribution of patients from low, medium, and high IHDI countries vs. Very high IHDI countries: vigiPoint analysis. Case count refers to the total number of reports during the study period for each specific IHDI group, categorized by covariate groups. Very High IHDI Group includes countries with an IHDI value above 0.800; High IHDI Group includes countries with values between 0.700 and 0.799; Medium IHDI Group includes values between 0.550 and 0.699; and Low IHDI Group includes countries with IHDI values below 0.550.

Patient's Sex & Age	Very High IHDI Group	Low IHDI Group		Medium IHDI Group		High IHDI Group	
	Case count (%)	Case count (%)	OR	Case count (%)	OR	Case count (%)	OR
Female	10290992 (60.95)	414322 (50.86)	0.66	1905423 (56.0)	0.82	459219.0 (60.97)	1.00
Male	6594432 (39.05)	400342 (49.14)	1.51	1497180 (44.0)	1.23	293961.0 (39.03)	1.00
Unknown sex	1426686 (7.79)	27584 (3.28)	0.40	38916 (1.13)	0.14	36878.0 (4.67)	0.58
28 days to 23 months	302998 (2.6)	32457 (4.25)	1.66	136594 (4.14)	1.62	23221.0 (3.46)	1.34
2 to 11 years	411041 (3.53)	44396 (5.81)	1.69	189652 (5.75)	1.67	30983.0 (4.61)	1.32
18 to 44 years	2666602 (22.90)	327137 (42.81)	2.52	932333 (28.26)	1.33	159137.0 (23.68)	1.05
65 to 74 years	2123045 (18.23)	65628 (8.59)	0.42	495848 (15.03)	0.79	121826.0 (18.13)	0.99
More than 75 years	1712914 (14.71)	25340 (3.32)	0.20	351420 (10.65)	0.69	103072.0 (15.34)	1.05
Unknown age	6665997 (36.4)	78018 (9.26)	0.18	141825 (4.12)	0.08	118141.0 (14.95)	0.31

A higher proportion of reports in the low IHDI group were submitted by physicians and pharmacists compared to the very high IHDI group (47.86%/18.76% vs. 29.34%/9.25%). In contrast, reports from consumers or non-healthcare professionals were significantly higher in the very high IHDI group than in the low IHDI group (46.85% vs. 14.38%). Reports lacking notifier information were also more common in the very high IHDI group compared to the low IHDI group (7.77% vs. 1.64%). The medium IHDI group had a higher proportion of reports with missing notifier information compared to the very high IHDI group (71.55% vs. 7.77%) and a significantly greater share of reports submitted by pharmacists (35.36% vs 9.23%). In comparison to the very high IHDI group, the high IHDI group had a higher proportion of reports from physicians (46.85% vs. 28.62%) but fewer reports from consumers, other health professionals, and lawyers (18.98% vs. 11.81%, 46.85% vs. 28.62%,

and 2.72% vs. 0.03%, respectively). Reports with unknown notifiers were less frequent in the high IHDI group than in the very high IHDI group (2.43% vs. 7.77%) (Table 3).

Table 3. Key features of notifier of ICSRs for low, medium and high IHDI countries compared with very high IHDI countries: vigiPoint Analysis. Case count refers to the total number of reports during the study period for each specific IHDI group, categorized by covariate groups. Very High IHDI Group includes countries with an IHDI value above 0.800; High IHDI Group includes countries with values between 0.700 and 0.799; Medium IHDI Group includes values between 0.550 and 0.699; and Low IHDI Group includes countries with IHDI values below 0.550.

Notifier	Very High IHDI Group	Low IHDI Group		Medium IHDI Group		High IHDI Group	
	Case count (%)	Case count (%)	OR	Case count (%)	OR	Case count (%)	OR
Consumers	7912288 (46.85)	119141 (14.38)	0.19	129927 (13.27)	0.17	220601 (28.62)	0.46
Pharmacist	1563098 (9.25)	155381 (18.76)	2.26	346180 (35.36)	5.36	99923 (12.96)	1.46
Physician	4956173 (29.34)	396510 (47.86)	2.21	376299 (38.43)	1.50	394269 (51.15)	2.52
Other Health Professional	3205089 (18.98)	195187 (23.56)	1.32	148904 (15.21)	0.77	91000 (11.81)	0.57
Lawyer	458662 (2.72)	101 (0.01)	0.00	1183 (0.12)	0.04	233 (0.03)	0.01
Unknown	1422511 (7.77)	13853 (1.64)	0.20	2462426 (71.55)	29.86	19230 (2.43)	0.30

The very high IHDI group had a larger proportion of reports with a vigiGrade score below 0.8 (indicating low completeness) compared to the low and high IHDI groups (82.33% vs. 43.55% and 57.73%, respectively). In both the medium and high IHDI groups, the proportion of non-fatal reports was higher compared to the very high IHDI group (98.52% vs. 94.75% and 96.46% vs. 94.75%, respectively). The proportion of reported serious cases was significantly lower in the low and medium IHDI groups compared to the very high IHDI group (39.67% vs 26.08% and 23.88%) (Table 4).

Table 4. Low, medium and high IHDI countries ICSRs seriousness and vigiGrade completeness score compared to very high IHDI countries: vigiPoint Analysis. Classification based on completeness was determined using the vigiGrade score, where scores below 0.8 indicate low completeness and scores above 0.8 indicate high completeness. Case count refers to the total number of reports during the study period for each IHDI group, categorized by covariate groups. Very High IHDI Group includes countries with an IHDI value above 0.800; High IHDI Group includes countries with values between 0.700 and 0.799; Medium IHDI Group includes values between 0.550 and 0.699; and Low IHDI Group includes countries with IHDI values below 0.550.

Reported Cases	Very High IHDI Group	Low IHDI Group		Medium IHDI Group		High IHDI Group	
	Case count (%)	Case count (%)	OR	Case count (%)	OR	Case count (%)	OR
Low completeness	15057019 (82.33)	366558 (43.55)	0.17	2963956 (86.45)	1.37	456042 (57.73)	0.29
High completeness	3232216 (17.67)	475202 (56.45)	6.04	464601 (13.55)	0.73	333871 (42.27)	3.41
Not reported fatal	17350175 (94.75)	805538 (95.64)	1.22	3390663 (98.52)	3.70	762119 (96.46)	1.51
Reported fatal	961935 (5.25)	36710 (4.36)	0.82	50856 (1.48)	0.27	27939 (3.54)	0.66
Non-serious (E2B only)	10707517 (60.33)	607604 (73.92)	1.86	615344 (76.12)	2.10	423958 (55.48)	0.82
Serious (E2B only)	7040096.0 (39.67%)	214404.0 (26.08%)	0.54	193035 (23.88)	0.48	340261 (44.52)	1.22

Reports from clinical studies were more frequent in the very high IHDI group than in the low (15.93% vs. 11.08%) and medium (15.93% vs. 6.05%) IHDI groups. Reports from post-marketing surveillance were notably higher in the medium IHDI group compared to the very high IHDI group (5.13% vs 0.02%). Reports lacking information on report type were more common in the very high IHDI group compared to the low (1.2% vs. 0.05%) and high (1.2% vs. 0.01%) IHDI groups but were significantly more prevalent in the medium IHDI group (1.17% vs. 61.26%) (Table 5).

Table 5. ICSRs source type for low, medium and high IHDI countries compared with very high IHDI countries: vigiPoint Analysis. Report type refers to the source of Individual Case Safety Reports (ICSRs) and their generation origins. PMS/Special monitoring refers to Post-Marketing Surveillance and other active surveillance strategies. Case count represents the total number of reports during the study period for each IHDI group, categorized by covariate groups. Very High IHDI Group includes countries with an IHDI value above 0.800; High IHDI Group includes countries with values between 0.700 and 0.799; Medium IHDI Group includes values between 0.550 and 0.699; and Low IHDI Group includes countries with IHDI values below 0.550.

Report Type	Very High IHDI Group	Low IHDI Group		Medium IHDI Group		High IHDI Group	
	Case count (%)	Case count (%)	OR	Case count (%)	OR	Case count (%)	OR
Report from clinical study	2883705 (15.93)	93281 (11.08)	0.66	80690 (6.05)	0.34	164686 (20.85)	1.39
PMS/Special Monitoring	3310 (0.02)	996 (0.12)	6.48	68346 (5.13)	295.38	1374 (0.17)	9.53
Not Available	213612 (1.17)	415 (0.05)	0.04	2108235 (61.26)	133.97	116 (0.01)	0.01
Other	224996 (1.24)	12917 (1.53)	1.24	48331 (3.62)	2.99	4807 (0.61)	0.49

Drugs used to treat tuberculosis were reported more frequently in Low IHDI countries (5.22%) compared to Very High IHDI countries (0.23%). Similarly, direct-acting antivirals (10.66% vs. 2.03%) and anti-infectives (7.8% vs. 2.35%) were more commonly reported in Low IHDI countries. In contrast, Very High IHDI countries had higher reporting for immunosuppressants (17.19% vs. 3.48%), opioids (4.36% vs. 1.55%), lipid-modifying agents (3.53% vs. 1.18%), drugs for peptic ulcer and gastro-esophageal disease (2.87% vs. 1.13%), and medications used in addictive disorders (2.2% vs. 0.58%). In Medium IHDI regions, higher usage of other beta-lactam antibiotics (10.35% vs. 1.16%), anti-infectives (10.08% vs. 2.35%), and penicillin-based antibiotics (6.04% vs. 1.23%) were observed. In contrast, in Very High IHDI regions, immunosuppressants (17.19% vs. 2.26%), drugs used in addictive disorders (2.2% vs. 0.17%), protein kinase inhibitors (3.45% vs. 1.08%), and hormonal contraceptives (2.14% vs. 0.48%) were reported more frequently. In Very High IHDI regions, opioids were used more (4.36% vs. 1.82%), as well as treatments for addictive disorders (2.2% vs. 0.63%) and drugs for peptic ulcer and gastro-oesophageal reflux disease (3.53% vs. 1.19%). In High IHDI regions, there was higher usage of anti-infectives (4.31% vs. 2.35%), penicillin-based antibiotics (2.52% vs. 1.23%), and monoclonal antibodies (4.07% vs. 2.26%) (Table 6).

Table 6. Relative reporting of top 5 suspected drug groups in low, medium and high IHDI countries compared with very high IHDI countries: vigiPoint Analysis. Suspected Drug Group (SpATClvl3) refers to the classification of reported drugs according to the Anatomical Therapeutic Chemical (ATC) system at the third level. Case count represents the total number of reports during the study period for each IHDI group, categorized by covariate groups. Very High IHDI Group includes countries with an IHDI value above 0.800; High IHDI Group includes countries with values between 0.700 and 0.799; Medium IHDI Group includes values between 0.550 and 0.699; and Low IHDI Group includes countries with IHDI values below 0.550.

Suspected Drug Group (SpATClvl3)	Very High IHDI Case count (%)	Low IHDI Case count (%)	OR
Higher Relative Reporting Rates in Low IHDI			
DRUGS FOR TREATMENT OF TUBERCULOSIS [J04A]	41555.0 (0.23)	43941.0 (5.22)	24.20
DIRECT ACTING ANTIVIRALS [J05A]	372433.0 (2.03)	89823.0 (10.66)	5.75
ANTIINFECTIVES [S01A]	430503.0 (2.35)	65696.0 (7.80)	3.51
OTHER ANTIBACTERIALS [J01X]	143129.0 (0.78)	30713.0 (3.65)	4.80
ANTIBIOTICS FOR TOPICAL USE [D06A]	248341.0 (1.36)	42620.0 (5.06)	3.88
Lower Relative Reporting Rates in Low IHDI			
IMMUNOSUPPRESSANTS [L04A]	3148222.0 (17.19)	29290.0 (3.48)	0.17
IMMUNOSTIMULANTS [L03A]	496231.0 (2.71)	6146.0 (0.73)	0.26
OPIOIDS [N02A]	798502.0 (4.36)	13058.0 (1.55)	0.35
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) [A02B]	646241.0 (3.53)	9952.0 (1.18)	0.33
DRUGS USED IN ADDICTIVE DISORDERS [N07B]	403671.0 (2.20)	4881.0 (0.58)	0.26
Suspected Drug Group (SpATClvl3)	Very High IHDI Case count (%)	Medium IHDI Case count (%)	OR
Higher Relative Reporting Rates in Medium IHDI			
OTHER BETA-LACTAM ANTIBACTERIALS [J01D]	212850.0 (1.16)	356043.0 (10.35)	9.81
ANTIINFECTIVES [S01A]	430503.0 (2.35)	347022.0 (10.08)	4.66
BETA-LACTAM ANTIBACTERIALS, PENICILLINS [J01C]	225001.0 (1.23)	208001.0 (6.04)	5.17
QUINOLONE ANTIBACTERIALS [J01M]	150346.0 (0.82)	148278.0 (4.31)	5.44
I.V. SOLUTIONS [B05B]	108022.0 (0.59)	121866.0 (3.54)	6.19
Lower Relative Reporting Rates in Medium IHDI			
IMMUNOSUPPRESSANTS [L04A]	3148222.0 (17.19)	77762.0 (2.26)	0.11
DRUGS USED IN ADDICTIVE DISORDERS [N07B]	403671.0 (2.20)	5773.0 (0.17)	0.08
PROTEIN KINASE INHIBITORS [L01E]	631852.0 (3.45)	37035.0 (1.08)	0.30
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE [G03A]	391274.0 (2.14)	16396.0 (0.48)	0.22
CONTRACEPTIVES FOR TOPICAL USE [G02B]	263369.0 (1.44)	6311.0 (0.18)	0.13

Suspected Drug Group (SpATClvl3)	Very High IHDI Case count (%)	High IHDI Case count (%)	OR
Higher Relative Reporting Rates in High IHDI			
ANTIINFECTIVES [S01A]	430503.0 (2.35)	34043.0 (4.31)	1.87
BETA-LACTAM ANTIBACTERIALS, PENICILLINS [J01C]	225001.0 (1.23)	19903.0 (2.52)	2.08
OTHER DIAGNOSTIC AGENTS [V04C]	162152.0 (0.89)	15571.0 (1.97)	2.25
MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES [L01F]	413183.0 (2.26)	32141.0 (4.07)	1.84
ACE INHIBITORS, PLAIN [C09A]	88895.0 (0.49)	10161.0 (1.29)	2.67
Lower Relative Reporting Rates in High IHDI			
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) [A02B]	646241.0 (3.53)	9408.0 (1.19)	0.33
DRUGS USED IN ADDICTIVE DISORDERS [N07B]	403671.0 (2.20)	4986.0 (0.63)	0.28
OPIOIDS [N02A]	798502.0 (4.36)	14372.0 (1.82)	0.41
OTHER ANTIHYPERTENSIVES [C02K]	232798.0 (1.27)	2898.0 (0.37)	0.29
ANESTHETICS, GENERAL [N01A]	265036.0 (1.45)	3824.0 (0.48)	0.33

Reporting of drug ineffectiveness was significantly higher in the very high IHDI group compared to the low and medium IHDI group (5.14% vs 1.50% & 0.77%). In the Low IHDI group, vomiting (6.79% vs. 2.96%), gastritis (1.16% vs. 0.09%), pyrexia (5.20% vs. 2.46%), anemia (1.89% vs. 0.69%), and rash maculopapular (0.99% vs. 0.2%) were reported more often. Conversely, in the very high IHDI group, drug ineffectiveness (5.14% vs. 1.50%), product dose omission issue (1.82% vs 0.17%), fatigue (3.44% vs. 1.09%), pain (2.75% vs. 0.85%), and malaise (1.97% vs. 0.49%) occurred more frequently. In the Very High vs. Medium IHDIs comparison, the Medium IHDI group reported higher rates of chest pain (5.49% vs. 0.76%), myelosuppression (2.65% vs. 0.03%), rash maculopapular (2.69% vs. 0.2%), pruritus (11.05% vs. 3.24%), and chills (4.3% vs. 0.8%). The Very High IHDI had higher rates of drug ineffectiveness (5.14% vs. 0.77%), fatigue (3.44% vs. 0.61%), death (2.4% vs. 0.4%), off-label use (2.3%), and dose omission (0.37%). In the Very High vs. High IHDI comparison, erythema (3.0% vs. 1.51%) and neutropenia (1.39% vs. 0.63%) were more frequent in the High IHDI, while the Very High IHDI reported higher rates of dose omission (1.82% vs. 0.34%), death (2.4% vs. 0.87%), drug dependence (0.76% vs. 0.09%), and fatigue (3.44% vs. 1.95%) (Table 7).

Table 7. Relative reporting of top 5 specific adverse events (AE) MedDRA preferred Terms in low, medium and high IHDI countries compared with very high IHDI countries: vigiPoint Analysis. Reported Events (MedDRA PT) refer to adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA) at the Preferred Term (PT) level, aggregated from higher-level terms. Case count represents the total number of reports during the study period for each IHDI group, categorized by covariate groups. Very High IHDI Group includes countries with an IHDI value above 0.800; High IHDI Group includes countries with values between 0.700 and 0.799; Medium IHDI Group includes values between 0.550 and 0.699; and Low IHDI Group includes countries with IHDI values below 0.550.

Reported Events (MedDRAPT)	Very High IHDI Case count (%)	Low IHDI Case count (%)	OR
Higher Relative Reporting Rates in Low IHDI			
Vomiting	541817.0 (2.96)	57180.0 (6.79)	2.39
Gastritis	16802.0 (0.09)	9744.0 (1.16)	12.75
Pyrexia	450253.0 (2.46)	43758.0 (5.20)	2.17
Anaemia	126283.0 (0.69)	15919.0 (1.89)	2.77
Rash maculo-papular	37229.0 (0.20)	8360.0 (0.99)	4.92
Lower Relative Reporting Rates in Low IHDI			
Drug ineffective	940965.0 (5.14)	12609.0 (1.50)	0.28
Product dose omission issue	333364.0 (1.82)	1469.0 (0.17)	0.09
Fatigue	629301.0 (3.44)	9160.0 (1.09)	0.31
Pain	503241.0 (2.75)	7169.0 (0.85)	0.30
Malaise	359931.0 (1.97)	4153.0 (0.49)	0.25
Reported Events (MedDRAPT)	Very High IHDI Case count (%)	Medium IHDI Case count (%)	OR
Higher Relative Reporting Rates in Medium IHDI			
Chest pain	138501.0 (0.76)	188995.0 (5.49)	7.63
Myelosuppression	6400.0 (0.03)	91350.0 (2.65)	77.99
Rash maculo-papular	37229.0 (0.20)	92669.0 (2.69)	13.58
Pruritus	594178.0 (3.24)	380142.0 (11.05)	3.70
Chills	146280.0 (0.80)	148088.0 (4.3)	5.58
Lower Relative Reporting Rates in Medium IHDI			
Drug ineffective	940965.0 (5.14)	26332.0 (0.77)	0.14
Fatigue	629301.0 (3.44)	21025.0 (0.61)	0.17
Death	439097.0 (2.40)	13849.0 (0.40)	0.16
Off label use	421608.0 (2.30)	12672.0 (0.37)	0.16
Product dose omission issue	333364.0 (1.82)	5810.0 (0.17)	0.09
Reported Events (MedDRAPT)	Very High IHDI Case count (%)	High IHDI Case count (%)	OR
Higher Relative Reporting Rates in High IHDI			

Erythema	276415.0 (1.51)	23675.0 (3.0)	2.02
Neutropenia	116260.0 (0.63)	10956.0 (1.39)	2.20
Lower Relative Reporting Rates in High IHDI			
Product dose omission issue	333364.0 (1.82)	2669.0 (0.34)	0.18
Death	439097.0 (2.4)	6899.0 (0.87)	0.36
No adverse event	156242.0 (0.85)	869.0 (0.11)	0.13
Drug dependence	139286.0 (0.76)	714.0 (0.09)	0.12
Fatigue	629301.0 (3.44)	15373.0 (1.95)	0.56

4 DISCUSSIONS

4.1 Impact of IHDI and its dimensions on ICSRs reporting rates

To the best of our knowledge, this is the first study to explore the relationship between countries' IHDI and their ICSR reporting patterns on a global scale. Our analysis showed a positive correlation between ADR reporting rates and the IHDI, as well as with each of its three-dimensional indices: health, education, and income. These associations, along with the multicollinearity among the three indices and with the IHDI itself, help explain the overall positive relationship observed between IHDI and ADR reporting rates.

As previously reported by Aagaard et al. (2012), high-income countries exhibited the highest ADR reporting rates, ranging from 3 to 613 reports per million people per year, while low-income countries reported between 0 and 21 cases per million annually. These findings are consistent with our study. This difference may be explained by the fact that, although many low- and middle-income countries have national pharmacovigilance systems, they often struggle with weak regulatory enforcement and limited awareness among healthcare professionals, resulting in lower reporting rates (Kiguba et al., 2023) .

The present study also found that countries with higher health index values tended to have higher reporting rates, which may reflect the prioritization of healthcare systems and a greater capacity for monitoring and reporting ADRs. This observation aligns with earlier

research showing that both healthcare expenditure and the strength of a healthcare system significantly influence population life expectancy (Rafia et al., 2023). Together, these findings highlight the essential role of well-developed health systems in supporting effective pharmacovigilance activities. In addition, a positive link between education levels and ADR reporting rate was found. This could be because people in countries with higher education tend to have better health literacy, which makes them more likely to understand health-related information and take part in healthcare processes, like reporting adverse drug reactions. A population-based survey from Denmark supports this idea, showing that education is closely tied to health literacy (Bo et al., 2014). People with lower education levels often struggled more with understanding health information and communicating with healthcare providers compared to individuals with higher education levels. This is further supported by a cross-sectional study from Japan, which found that individuals with higher health literacy were more likely to comprehend medication package inserts and consult healthcare professionals regarding adverse drug events compared to those with lower health literacy (Masumoto et al., 2023). Consequently, the present evidence implies that better-educated individuals are more capable of recognizing and reporting ADRs, contributing to higher national reporting rates.

It is, however, important to interpret the above discussed individual associations with caution due to the inherent multicollinearity among the income, health, and education indices. These dimensions are often interrelated, for instance, national income influences both access to education and quality of healthcare, while education can in turn affect health outcomes (Marmot, 2005). As a result, the observed relationships likely reflect the combined effect of a country's broader socioeconomic context.

4.2 Characteristics of ICSRs in low, medium, high IHDI compared to very high IHDI

In low and medium IHDI countries, ICSRs were predominantly submitted by pharmacists and physicians, while patients or consumers were underrepresented. In high IHDI countries,

physicians were identified the primary contributors. However, in very high IHDI countries, consumers accounted for the majority of reports. This shift is likely due to the presence of systems that enable patients to report ADRs directly to their National Competent Authorities (Icelandic Medicines Agency, n.d.; Margraff & Bertram, 2014). Furthermore, the advanced pharmacovigilance systems in high income countries significantly improve the effectiveness of this patient-centered reporting framework (Kiguba et al., 2023; Margraff & Bertram, 2014).

The completeness of case safety reports tended to be lower in very high IHDI countries compared to low and high IHDI countries. Several factors may contribute to this. One contributing factor is the potential loss of information during the transfer from national databases to the UMC, whether intentional or unintentional. A 2013 study by the UMC found that only 13.0% of global reports submitted between 2007 and 2012 were considered well documented, highlighting the issue of incomplete data (Bergvall et al., 2014). Additionally, critical details may be included in the comments section instead of the designated fields, leading to gaps in the structured data (Wakao et al., 2019). Another notable factor is the absence of narratives in many reports from the United States—a very high IHDI country—submitted to VigiBase. Since the USA contributes a substantial volume of reports (Wakao et al., 2019), this omission may partly explain the observed discrepancy. This points to a combined limitation of vigiGrade (which rewards reports with narratives) and of VigiBase itself, given that countries have discretion over which data elements they choose to submit (Bergvall et al., 2014). These findings point to the importance of standardizing data entry practices and improving reporting workflows, both within national systems and in the context of international data sharing. Enhancing consistency in how information is recorded and transferred can help reduce data loss and improve the overall quality and usability of pharmacovigilance data.

Differences were observed in the reporting of fatal and serious AEs across countries with varying IHDI levels. These differences may not necessarily reflect true variations in the severity of ADRs but could be influenced by how countries document and classify these

events. Some countries may follow specific reporting guidelines that affect whether serious outcomes, such as death, are recorded directly as AEs or in other parts of the report. These variations in reporting practices can impact the interpretation of pharmacovigilance data. A similar pattern was observed in previous research, which found that Japan reported fewer deaths as AE terms, but when other reporting elements were considered, the actual rate of fatal outcomes was similar to that in other countries (Wakao et al., 2019). These findings suggest that differences in reporting practices should be explored further to better understand how they might influence global reporting trends.

ICSRs from clinical studies were significantly underrepresented in low and medium IHDI countries. A systematic review found limited clinical studies in low- and middle-income countries despite high disease burdens (Alemayehu et al., 2018). Contributing factors include inadequate funding, lack of skilled personnel, weak ethical and regulatory systems, poor research infrastructure, operational challenges, and competing healthcare priorities. However, these challenges have not been thoroughly examined in relation to a country's position on the human development scale. Case reports originating from special monitoring programs—such as active surveillance strategies and cohort event monitoring—were more common in medium IHDI countries than in very high IHDI countries. This trend appears to be largely driven by China, a medium IHDI country, which has implemented extensive active surveillance initiatives (X. Li et al., 2018).

The differences in drug reporting across IHDI regions reveal distinct patterns in drug usage and healthcare priorities. In lower IHDI countries, there is a higher focus on reporting drugs for infectious diseases, reflecting the substantial burden of conditions like tuberculosis. According to the World Health Organization, low- and middle-income countries bear 98% of the global tuberculosis burden (World Health Organization, 2024). In contrast, high and very high IHDI countries seem to prioritize chronic and complex health conditions, with increased reporting of immunosuppressants, opioids, and lipid-modifying agents. A multimethod study found that despite the effectiveness of hyperlipidemia treatments, low- and middle-income countries struggle with consistent access to these medications, likely leading to

lower rates of ADR reporting for chronic condition drugs like lipid-lowering agents (C. Li et al., 2024) . This may also suggest that healthcare systems in the high human development region are more equipped to manage chronic conditions, leading to more specialized treatments and associated adverse event reports. Medium IHDI countries show similarities to lower IHDI regions in their emphasis on infectious disease treatments. A notable observation is the significantly higher proportion of reports related to drugs for addictive disorders in the very high IHDI group compared to the other three IHDI groups. This imbalance may be due to the unequal access to opioid medications, with high-income countries in the very high IHDI group stocking far more opioid medication than necessary. In contrast, LMICs have access to only a fraction of the opioids required for palliative care. Studies show that just 1% of opioid medicines, measured in opioid morphine equivalents, are distributed in countries where the poorest half of the global population live, while the wealthiest 10% of countries hold 90% of these medicines (Knaul, 2021). This significant disparity likely contributes to the higher rates of addiction-related drug reports seen in high-IHDI regions. However, there are no studies that specifically examine the availability of medicines from the perspective of a nation's overall human development.

The reporting patterns of AEs across different IHDI regions highlights significant differences. Observed differences in the types of AEs reported across IHDI regions align closely with the patterns of suspected drug use. In low IHDI countries, the higher reporting of AEs such as vomiting, pyrexia, and anaemia corresponds with increased use of anti-infective medications, including drugs for tuberculosis, antivirals, and topical antibiotics. These medications are typically associated with the treatment of infectious and acute conditions, which are more prevalent in lower-income settings. In contrast, very high IHDI countries report more AEs like drug ineffectiveness, fatigue, and dose omission—likely linked to the more widespread use of medications for chronic diseases (Aagaard et al., 2012; Amalba & Bugri, 2021).

5 LIMITATIONS

A limitation of this study is the potential discrepancy between the number of ICSRs submitted to VigiBase and those reported by national pharmacovigilance centres in individual countries, which may impact the visualization of the relationship between reporting rates and independent factors. However, the large volume of reports in VigiBase helps to mitigate this potential statistical issue. Additionally, to reduce bias, all ICSRs related to COVID-19 vaccines were excluded, given the study period coincided with the SARS-CoV-2 pandemic. Despite this, the use of other supplementary medications during this time may still influence the relationship between reporting rates and socioeconomic factors. Moreover, the availability and use of different medication classes across IHDI groups could vary, potentially affecting this association and contributing to differences in the characteristics of reports submitted across these groups. Finally, general limitations of VigiBase data make it difficult to determine causality between events and medicinal products.

6 CONCLUSIONS

This is the first study to explore the global association between IHDI and ICSR reporting. We found a strong positive correlation between ADR reporting rates and the IHDI, including its components: income, health, and education - key indicators of a country's socioeconomic status that support effective pharmacovigilance. We also identified clear differences in reporting trends across countries with different IHDI levels. Higher-IHDI countries showed more active consumer participation in ADR reporting, likely due to established systems and policies, whereas lower-IHDI countries contributed fewer ICSRs from clinical studies, indicating research infrastructure gaps. Notably, the completeness of case reports was often lower in very high IHDI countries, highlighting a key area for improvement even in well-resourced systems.

Socioeconomic factors significantly influence these patterns, but behavioural aspects like awareness and willingness to report may also play a role. Future research should explore how these factors interact to affect ADR reporting, which is vital for enhancing pharmacovigilance, especially in developing healthcare systems.

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MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA® trademark is registered by ICH.

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8 ANNEXES

8.1 Multicollinearity Assessment Among Independent Variables Using Variance Inflation Factor

Table A. Variance Inflation Factor (VIF) Results for Inequality-Adjusted Human Development Indices

Variables	VIF value
Inequality-Adjusted Human Development Index	1089.3
Inequality-Adjusted Life Expectancy Index	78.4
Inequality-Adjusted Income Index	145.3
Inequality-Adjusted Education Index	205
Constant	23.2