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LEADING ARTICLE

VigiBase: Resource Profile Update with a Summary of Global Patterns and Trends in Adverse Event Reports for Medicines and Vaccines

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Abstract

VigiBase, the WHO global database of adverse event reports for medicines and vaccines, receives information on suspected adverse effects of medicinal products from countries, regions and territories that are members of the WHO Programme for International Drug Monitoring. The database serves as a global resource for pharmacovigilance signal management and scientific development. Its initial establishment through the programme in 1968 has also contributed to the international harmonisation of adverse event report data. As of 31 December 2024, the database includes over 40 million individual case reports coded in standard terminologies (WHODrug and MedDRA®). These reports, of which ~80% relate to medicines and ~20% to vaccines, come from over 160 countries. This profile paper aims to provide an update on the database infrastructure including data capture, management and analysis tools. It also presents a summary of global patterns and trends of key report characteristics, as well as strengths and limitations of the data to offer context to users and the global pharmacovigilance community.

Key Points

VigiBase is the world's largest collection of adverse event reports supporting global pharmacovigilance activities by enabling international comparisons and harmonisation of the data.

Contributions to the database from previously underrepresented geographic areas (especially Asia) and types of reporters (non-physicians) have increased over time.

Heterogeneity in healthcare systems and reporting practices is inherently greater in a global context than at regional or national levels and must be considered when using the data for signal management and scientific development.

1 Introduction

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other problem related to medicines or vaccines (henceforth referred to as medicinal products) [1]. The World Health Organization Programme for International Drug Monitoring (WHO PIDM), launched in 1968, is an international collaboration aimed at advancing the safe use of medicinal products by promptly identifying safety concerns, and ensuring that this information is disseminated and acted upon. The member organisations of the WHO PIDM operate at the national level and collaborate globally to monitor and identify possible adverse effects of medicinal products, while contributing to the development of worldwide pharmacovigilance standards and systems. As part of the programme, members submit and share data with each other through VigiBase, the WHO global database of adverse event (AE) reports for medicines and vaccines, which has been maintained by the Uppsala Monitoring Centre (UMC), in Sweden, since 1978 [2].

While the scope of data available for pharmacovigilance activities has expanded over time [3, 4], collections of AE reports continue to be a cornerstone in identifying and assessing new safety concerns in pharmacovigilance

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signal management. Their analysis informs most regulatory decisions related to signals [5, 6], i.e., information that suggests a possible causal relationship between a medicinal product and an AE [7, 8]. The need for global data sharing through international collaboration became evident as early as the 1960s, following the thalidomide disaster [9]. The pooling of reports in VigiBase strengthens the ability to study rare AEs, which may not be feasible in national or regional databases due to smaller report volumes. The broad geographic coverage of the data also supports comprehensive signal analysis, across regions and countries.

Today, VigiBase mainly serves as a global resource for pharmacovigilance signal assessment and scientific development including methods for analysing AE data. A notable example of a signal assessed using VigiBase is the risk of neonatal withdrawal syndrome following maternal use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy [10]. The size of the database further enables the analysis of signals that may only become apparent under certain circumstances, such as signals emerging from drug-drug interactions [11] or in specific at-risk population groups [12]. VigiBase has also contributed to signal detection, with risks of myocardial infarction with abacavir [13], and tachycardia with cisapride [14], being illustrative examples. Additionally, because of its coverage VigiBase could potentially support the identification of other product-related issues that occur in clusters over time and across geographic areas, such as suspected substandard medicines [15, 16], and medication errors [17], although performing root cause analysis for these problems can be challenging and practical use is yet to be determined. Lastly, beyond assessing signals or other medicinal product-related issues, the data may be used for characterizing suspected adverse effects in terms of their temporality, dose-relation, reversibility and outcome in terms of seriousness. These insights are important from a clinical perspective and can inform the design of follow-up epidemiological studies to study these aspects in more detail.

Since its inception, VigiBase has grown significantly, surpassing 56 million processed reports as of 31 December 2024. This total represents around 40 million unique cases (after accounting for follow-up and suspected duplicate reports) with roughly 80% relating to medicines and 20% to vaccines. The efforts to enable global sharing of data, as part of the programme, has also contributed to the harmonisation of AE data alongside initiatives from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [18] and the Council for International Organizations of Medical Sciences (CIOMS) [19]. In parallel, scientific methods, tools and services developed by the UMC and available to users of VigiBase have expanded in recent years. Given that working with VigiBase requires a solid understanding of its structure and content, the aim of this paper is to present an up-to-date profile of this resource focusing on data capture and management, analysis tools, and key database characteristics. As VigiBase has evolved over time with the continuous accumulation of reports since the latest description of the data [20], the paper also highlights recent trends and developments, and addresses strengths and limitations of the data to provide context to users and the global pharmacovigilance community.

2 VigiBase Data Capture, Management and Tools

An overview of the VigiBase data flow, including the collection, processing and analysis of reports, is summarised in Fig. 1.

2.1 Data Collection

VigiBase is the world's largest database of AE reports for medicines and vaccines, bringing together reports from national pharmacovigilance databases of WHO PIDM members. The database includes data from the US FDA Adverse Event Reporting System (FAERS) for medicines [21] and the US Vaccine Adverse Event Reporting System (VAERS) [22] as well as data from countries across Asia, Africa, Latin America & Caribbean, Oceania, and from Europe (where, since 2017, many reports have been shared via EudraVigilance, the centralised European pharmacovigilance database for medicine and vaccine reports [23]). Due to the variable nature of AE reporting, which is influenced by local product availability, clinical and reporting practices, and legislative and regulatory requirements (i.e., factors that affect the collection, processing and sharing of reports by member organisations), the cases captured by the database naturally vary based on the origin of the reports. For instance, not all member organisations accept reports from the same spectrum of notifiers—with some centres not accepting reports submitted by consumers and others only contributing reports of serious AEs to VigiBase. Additionally, the amount and detail of information available for each case and the likelihood of a causal relationship between the reported AE and the medicinal product can vary depending on the source (both across and within PIDM member countries) due to varying reporting practices and legal frameworks governing data sharing. There are some members, for example, who collect any AE reported in patients exposed to a medicinal product, regardless of whether it is suspected to be related to the product. Also, the criteria for which medicinal products to include on the report and whether to classify them as suspected, interacting or concomitant, can vary between reporters and member organisations.

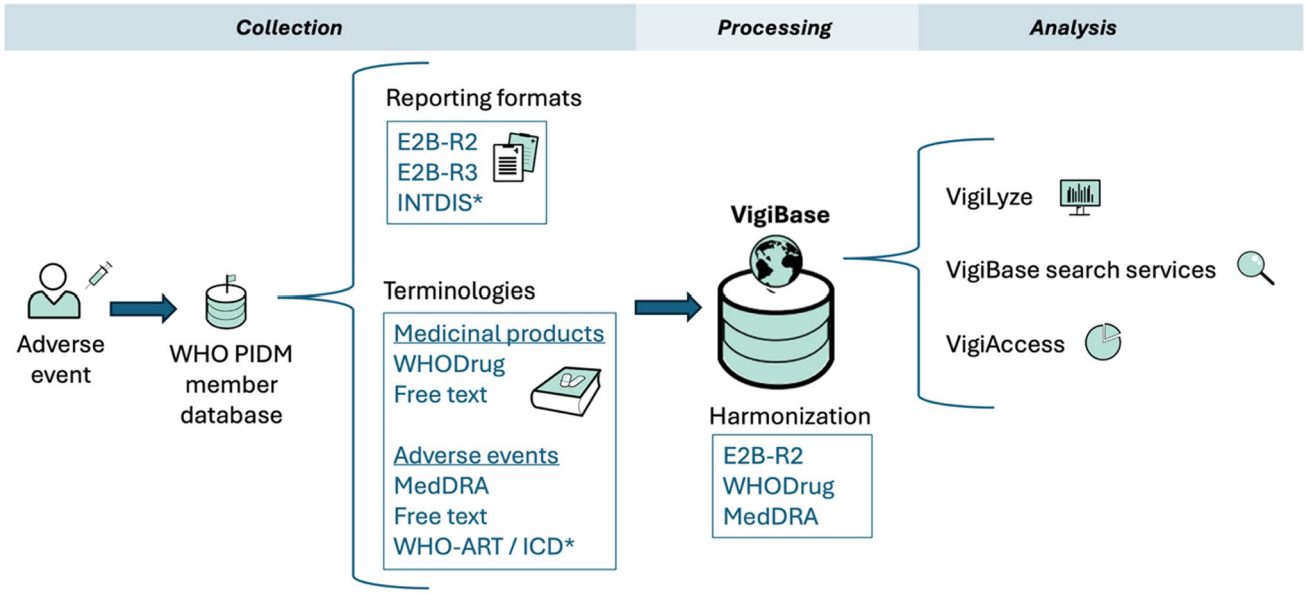

Fig. 1 Overview of VigiBase data flow capturing the collection, processing and analysis of the data. *Historical formats and formats of limited current use. *ICD* International Classification of Diseases, *INTDIS* international drug information system, *MedDRA*® Medical Dictionary for Regulatory Activities, *WHO-ART* WHO Adverse Reactions Terminology, *WHO PIDM* World Health Organization Programme for International Drug Monitoring

VigiBase is continually updated with new incoming reports and receives follow-up reports with updated information, which are linked to the original report. In some cases, previously received reports are removed from the database when they are nullified by the source (i.e., the PIDM member sharing the data), for example when a case has been found to be erroneous. Prompt report entry is important to minimise the lag time between the occurrence of a case and availability of the report in the global database, to enable timely signal management. All PIDM members are encouraged to share reports at least monthly, and many do so more frequently (for example reports are shared daily from EudraVigilance) while some only share reports when follow-up information is complete, which can cause delays.

The information that can be transferred to VigiBase for AE reports is largely governed by standard reporting formats, which have changed over time. Historically, the international drug information system (INTDIS) format, the original WHO reporting format, served as standard for reporting. Today, most member organisations share reports in the E2B format, released by ICH [18] in 1997, with subsequent second and third major revisions (R2, R3) released later. To standardise analyses, reports shared in INTDIS and ICH E2B (R3) are currently converted to a version closely resembling R2 following ICH's official standard [24]. However, since most reports received today are in R3, a process of upgrading all reports to this format is planned for 2026. Variations in reporting format and their implementation at the country level contribute to variations in information being captured over time and across countries. Examples of upgrades in information captured across reporting formats are the introduction of seriousness criteria, reports from consumers receiving a designated reporter qualification, and linkage elements facilitating the reporting of information for specific product-event combinations (e.g., time-to-onset and assessment of relatedness). Additional free text fields now also make it possible to capture more detailed information such as case narratives, medical history details and other relevant comments or assessments from the reporter.

In terms of data sharing, for any national data management system with capability to export reports using the international standard for the electronic transmission of E2B (R2) or (R3) reports, the transfer of the data from the member organisation to VigiBase can be automated (using the server-to-server option of the VigiBase API). Today, many countries use VigiFlow as their national safety surveillance system for collecting, analysing, monitoring, and sharing AE data. VigiFlow is supported by connected applications such as VigiMobile, which collects reports from the public and healthcare professionals, and VigiFlow eReporting for Industry, which marketing authorisation holders use to submit reports in the E2B format [25]. Reports from publicly available US databases (FAERS and VAERS) are imported by UMC staff on a quarterly basis.

2.2 Data Processing

At the UMC, all incoming data are subjected to standard processing procedures. All reports are checked against minimum requirements for database entry [a reporting country, a national case identification number (that does not identify the patient or reporter), at least one AE term and at least one medicinal product term]. These criteria align with the minimal criteria for a valid report outlined in the ICH E2D guidance [26]. Other non-mandatory but relevant data elements include patient demographics (such as age, sex, and medical history), product-related details (e.g., dose, strength, start and stop dates, and indication) and information concerning the AE (including seriousness, outcome, start and end dates, as well as de-challenge and rechallenge information). In general, reporting guidelines recommend providing as much information as possible at the time of the initial report, as the minimal fields for a valid report are insufficient for causality assessment.

For data harmonisation purposes, medicinal product information is encoded to UMC's Drug Dictionary, WHODrug Global, a global medicine and vaccine terminology [27]. WHODrug Global uses non-proprietary names when available, such as International Non-proprietary Name (INN), United States Adopted Names (USAN) or Japanese Accepted Names (JAN). All medicinal products in WHODrug Global are assigned one or several Anatomical Therapeutic Chemical (ATC) system codes (maintained by the WHO Collaborating Centre for Drug Statistics Methodology [28]) based on their active ingredients and intended use. These include official ATC codes capturing main therapeutic indications and UMC-assigned ATC codes capturing additional indications described in product labels. In addition to the ATC system, WHODrug Global also uses the Herbal ATC (HATC) classification system, developed and maintained by the UMC, for classifying herbal remedies. Adverse event information is encoded to MedDRA®, the Medical Dictionary for Regulatory Activities developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [29]. Most reports received via VigiFlow are already coded in WHODrug and MedDRA®; those received via other channels are also often coded in MedDRA®. When standard codes are unavailable, reports are automatically coded to WHODrug and MedDRA® using: (i) a combination of rule-based pre-processing and text matching; (ii) a knowledge base of historical encodings from verbatim text to the standard terminologies; and (iii) WHODrug Koda—UMC's custom-built coding engine for medicinal product information [30]. In the cases where automatic coding fails, human domain experts perform the coding. Standard mappings to MedDRA® exist for other terminologies including the WHO Adverse Reactions Terminology (WHO-ART), widely used in the past, and the International Classification of Diseases (ICD) [31], developed and maintained by the WHO. In addition to AE reporting, indications for product use can be provided by the reporter as MedDRA® terms (in E2B format) or ICD terms mapped to MedDRA®.

After routine coding and mapping procedures, reports undergo additional processing steps to further clean the data and facilitate downstream analysis as required. This includes: (i) identification of foreign reports (i.e., cases reported by a member country other than the country from where the AE was initially reported) as many of these are expected to be duplicates already present in the originating country records; (ii) identification of suspected duplicate reports flagged by the vigiMatch de-duplication algorithm which detects suspiciously similar pairs of reports using probabilistic pattern matching [32]; (iii) identification of reports that list medicinal products as concomitant only (i.e., not as suspected and/or interacting) and (iv) recoding information from key structured fields such as the calculation of time-to-onset (TTO) based on the reported product start and event onset date (if the time interval between the exposure and event onset is not specifically reported). Of note, based on UMC's overall assessment, the relative frequency of report duplication is substantially higher among foreign than non-foreign reports. Because the vigiMatch de-duplication method cannot reliably identify all duplicate cases among foreign reports (due to limited available information), and because these reports are expected to have already been captured by the countries where the AE occurred, both duplicate and foreign reports are generally excluded from analyses.

2.3 Data Analysis

Access to VigiBase is governed by the VigiBase Data Access Conditions established by the WHO after consultation with the WHO PIDM member organisations. Its use is supported by a Caveat document [33], which states the restrictions, limitations, and conditions relating to data released from VigiBase. The primary users of VigiBase are the WHO PIDM member organisations and UMC, but different levels of access are also available to other stakeholders [34]. Programme members can view a defined limited set of fields through VigiLyze [35], a web-based search and analysis tool displaying both aggregate overviews of case report series and line listings for any medicinal product-AE combination, supporting signal management activities including statistical signal detection and qualitative assessments. The VigiBase search services [36] make aggregate or case level data of selected fields available in line with the VigiBase Data Access Conditions, for method development, signal detection and assessment

and other pharmacovigilance assignments requested by, for example, marketing authorisation holders, contract research organisations, academia and researchers from other sectors. Fees for all VigiBase Services are set on a cost recovery basis to support operation and development of VigiBase, ensuring equitable access and value for users [36]. Lastly, those who wish to explore publicly available data can use VigiAccess [37] for high-level descriptive summaries of selected fields by active ingredient searches, either through a graphical user interface or via a more powerful application programming interface (API).

Over the years, the UMC has developed various methods and algorithms for data processing and analysis (see Table 1), all of which have been published in open, peer reviewed scientific journals. Some of these are integrated in VigiLyze and other services accessible to external users, such as information component (IC) disproportionality analysis [38, 39], vigiMatch [32], vigiGrade [40] and the VigiBase pregnancy algorithm [41]. VigiRank [42], an algorithm incorporating both disproportionate reporting and other qualitative parameters has been the basis for UMC's own signal detection in VigiBase since 2015.

3 VigiBase Descriptive Statistics

As of 31 December 2024, VigiBase included ~40 million individual case reports with a medicinal product listed as suspected and/or interacting from over 160 countries after applying standard exclusion criteria (see online resource, Fig. S1 for the flow of reports including processing steps leading to the final dataset used for analysis). Figure 2 summarises the accumulation of reports received by calendar year. Around 70% of all reports have been received in the past 10 years, and 40% in the past 5 years. The growth of the database since 1968 can be attributed in part to the expansion of the programme, which has enabled more countries to contribute reports to the database. More recent increases in report accumulation are also linked to the widespread adoption of digital reporting systems (including mobile applications), changes in legal requirements for reporting AEs, greater patient involvement in pharmacovigilance practices [48, 49] and heightened reporting during the COVID-19 vaccination campaigns.

As of 31 December 2024, most reports concern medicines (80.2%). The COVID-19 vaccines and non–COVID-19 vaccines represent 14.4% and 5.1% of the database, respectively. Only a small percentage (0.3%) of reports involve more than one of these three product categories.

Annual report counts by product type are summarised in Fig. 3. The rise in yearly submissions has been driven mainly by medicine reports, while submissions of vaccine reports have increased at a slower pace, with some fluctuations over time (most notably, in 2021, the massive influx of COVID-19 vaccine reports, which led to these reports making up most database entries for that year).

To describe the nature of VigiBase data, Table 2 summarises key characteristics of all reports related to medicines or vaccines specifically as of 31 December 2024. Overall,

Table 1 Overview of methods and algorithms developed by the UMC for processing and analysing VigiBase data

Method/algorithm	Description	References
Information Component (IC) disproportionality measure	Pairwise disproportionality measure using a shrinkage observed-to-expected ratio	[38, 39]
Omega interaction measure	Disproportionality measure for drug-drug-interactions using a shrinkage observed-to-expected ratio	[11]
vigiGrade	Information completeness algorithm assigning a completeness score to each report	[40]
vigiMatch	Deduplication algorithm detecting suspiciously similar pairs of reports using probabilistic pattern matching	[32]
vigiRank	Statistical signal detection algorithm that uses a predictive model based on overall reporting patterns report quality and content	[42]
vigiPoint	Statistical method for pinpointing differences across report characteristics when comparing subsets of the data	[43]
vigiGroup	Data-driven consensus clustering algorithm to identify reports with similar AEs based on co-reported AE terms	[44]
vigiVec	Data-driven method for identifying clinically related terms using semantic vector representations of AEs and products based on reporting patterns	[45, 46]
VigiBase unmasking algorithm	Algorithm for detecting influential outliers to uncover associations masked by extreme reporting rates	[47]
VigiBase pregnancy algorithm	Rule-based algorithm for identifying reports related to pregnancy exposures, with or without AEs, affecting the pregnant individual, foetus or newborn	[41]

AE adverse event, *UMC* Uppsala Monitoring Centre

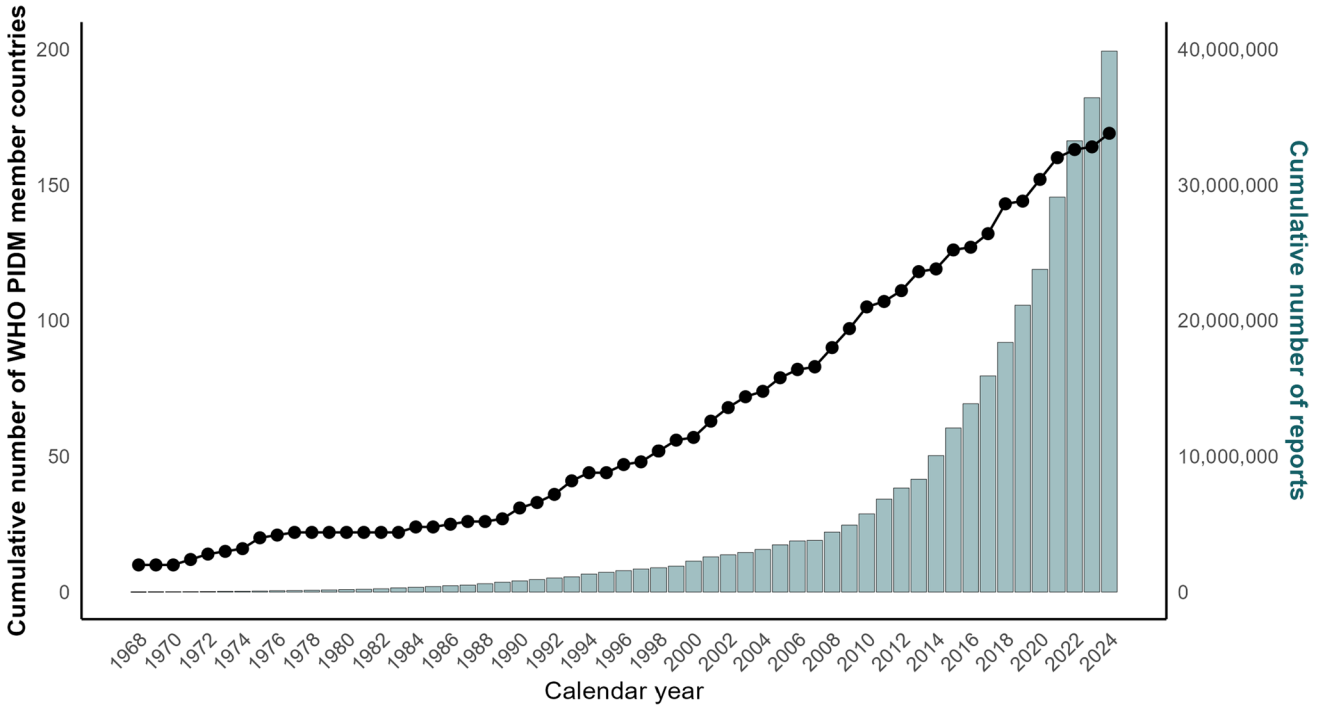

Fig. 2 Growth of VigiBase summarised by the cumulative number of reports with a suspected and/or interacting medicinal product in the database (bars) and number of WHO PIDM member countries sharing reports with VigiBase (dotted line), 1968–2024. The cumulative number of WHO PIDM member countries represents counts as observed over time since the inception of the database, including non-sovereign countries as of 2024 (British Virgin Islands (territory) and former Yugoslavia). *WHO PIDM* World Health Organization Programme for International Drug Monitoring

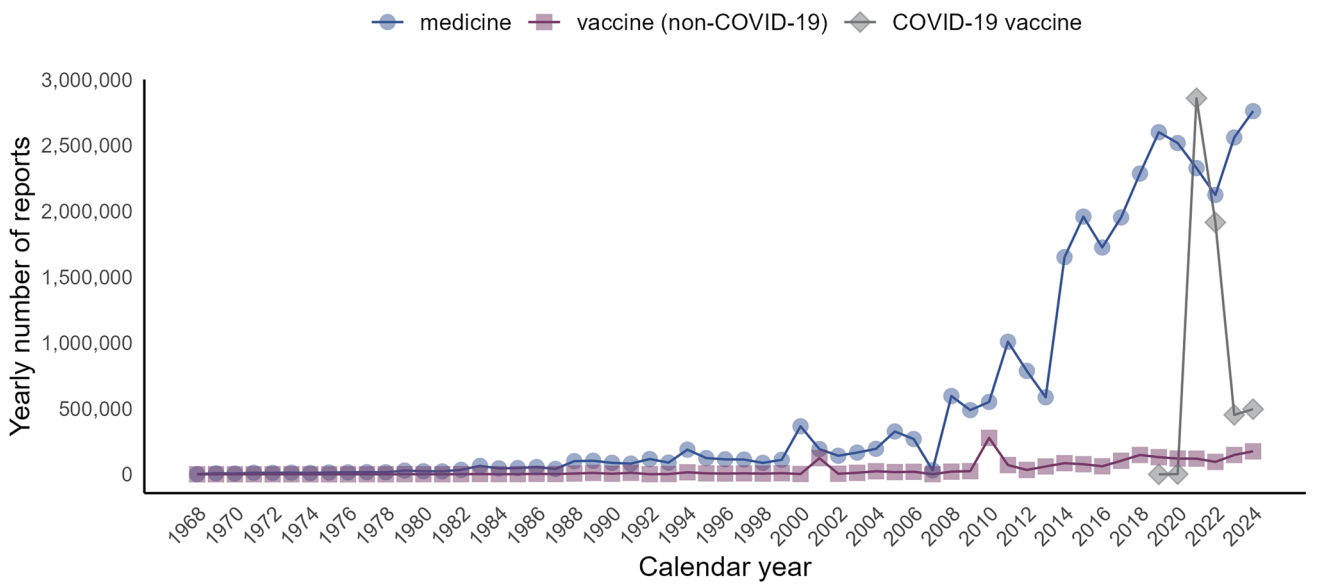

Fig. 3 Annual number of reports received in VigiBase by product type, 1968–2024. Reports listing medicines (circles) or vaccines (squares) specifically as suspected and/or interacting medicinal product. COVID-19 vaccine reports (diamonds) are shown separately to differentiate these reports from vaccine (non–COVID-19) reports. Reports involving several of these three product categories are not displayed

Table 2 Summary of report characteristics, overall and by product type

Characteristic, %	All ($N=39,861,516$)	Medicine ($N=31,961,877$)	Vaccine (non–COVID-19) ($N=2,056,862$)	COVID-19 vaccine ($N=5,722,913$)
Patient age[a]				
0–27 days	0.2	0.2	0.6	< 0.1
28 days to < 2 years	2.8	0.9	33.1	0.1
2–11 years	3.8	3.2	19.1	0.9
12–17 years	3.0	2.6	8.5	3.0
18–44 years	29.3	26.3	16.1	47.6
45–64 years	33.0	34.9	11.9	32.3
65–74 years	15.7	17.8	6.9	9.8
≥ 75 years	12.1	14.1	3.7	6.2
Missing	26.1	29.5	13.0	12.3
Patient sex				
Female	60.7	60.0	57.1	65.8
Male	39.3	40.0	42.9	34.2
Missing	6.2	7.2	3.0	1.2
Geographic area[b]				
USA & Canada	43.7	46.1	46.6	29.4
Europe	24.7	21.5	27.5	41.4
Asia	23.2	25.7	6.4	16.0
Latin America & Caribbean	4.2	3.9	5.3	5.4
Oceania	2.0	1.6	5.7	3.4
Africa	2.1	1.3	8.5	4.5
World Bank income groupings[c]				
High-income countries	82.0	81.3	82.6	85.7
Upper middle-income countries	13.0	14.5	7.2	6.4
Lower middle-income countries	4.5	4.0	8.0	6.0
Low-income countries	0.5	0.2	2.2	1.9
Report type				
Spontaneous[d]	86.4	84.0	95.2	95.9
Report from study	12.3	14.7	3.5	2.9
Other	1.3	1.3	1.3	1.2
Missing	6.7	8.4	0.1	< 0.1
Reporter qualification[e]				
Physician	31.4	33.0	42.2	17.0
Pharmacist	10.4	11.0	8.5	6.7
Other HCP	18.0	17.2	31.3	20.9
Lawyer	1.7	2.0	0.2	0.1
Consumer or other non-HCP	38.4	36.8	17.8	55.3
Missing	21.5	16.6	57.6	35.7
MAH report[f]	50.3	56.3	28.1	24.8
No. of medicinal products (active ingredients) reported as suspected and/or interacting[g]				
1	88.7	87.5	79.1	100.0
2–5	10.8	11.9	20.7	0.0
> 5	0.5	0.6	0.1	0.0
No. of AEs (preferred terms) reported[h]				
1	47.5	51.1	34.3	32.1
2–5	44.7	42.9	55.1	50.9
> 5	7.8	6.0	10.5	17.0
Seriousness criteria				
Death	3.5	4.1	0.7	1.2

Table 2 (continued)

Characteristic, %	All ($N=39,861,516$)	Medicine ($N=31,961,877$)	Vaccine (non–COVID-19) ($N=2,056,862$)	COVID-19 vaccine ($N=5,722,913$)
Life-threatening	1.5	1.6	1.2	1.4
Hospitalisation	11.1	12.0	8.1	7.1
Disabling	1.3	1.0	1.7	2.8
Congenital anomaly/birth defect	0.1	0.1	0.0	0.0
Other medically important condition	16.9	18.9	5.8	10.2
Reports with TTO[j]	59.1	52.5	83.6	86.9
Reports with dose information[j]	34.3	40.2	15.2	8.5
Reports with indication[j]	58.9	65.3	30.7	34.2

Distribution of characteristics of reports listing suspected and/or interacting medicinal products, overall and stratified by product type. Each product type category [medicine, vaccine (non-COVID-19) and COVID-19 vaccine] only includes products that exclusively belong to that category. Reports involving more than one of these three product categories have not been displayed in this table (0.3% of all reports)

For all variables, numbers (percentages) are given only for reports with no missing values to facilitate comparison of variable distributions across product types

GNI gross national income, *HCP* health care professional, *MAH* marketing authorisation holder, *PMS* postmarketing surveillance, *PTs* preferred terms, *TTO* time-to-onset

[a]Missingness on age includes reports where standard groupings of age do not apply (i.e., gestational age for reports concerning foetal cases)

[b]Based on grouping of countries specified in Table S1

[c]Based on 2024 World Bank's income classification of countries based on GNI per capita, except for Venezuela (non-classifiable in 2024 due to unavailability of data but classified as upper-middle income country in the table based on the most recent data available from the 2021 classification)

See also Table S2

[d]A spontaneous report is an unsolicited communication from a healthcare professional or consumer to a relevant authority or organisation, detailing one or more suspected AEs in a patient who was administered one or more medicinal products. It does not derive from a study or organised data collection system

[e]Reports with multiple reporter qualifications were assigned to each of the relevant qualifications

[f]All reports in VigiBase are shared by national regulatory authorities but may have been created either by a regulatory authority or MAH

[g]No. of unique active ingredient terms listed on a report

[h]No. of unique MedDRA® PTs listed on a report

[i]For each of these selected structured fields (TTO, dose information and indication), a report is considered valid if it contains at least 1 medicinal product- AE combination with a field value provided

most reports (90%) concern adults aged ≥ 18 years. Reports related to non–COVID-19 vaccines show a distinct age distribution, with ~ 60% of these reports involving neonates and children up until the age of 18 years, in line with common vaccination practices. Across the database, reports concerning females are over-represented (~ 60% of all reports) irrespective of product type. This may be attributed to women receiving more product prescriptions, engaging more frequently with healthcare services, and/or being more susceptible to AEs [50].

Geographically, most reports in the database originate from the North American region (USA and Canada) (44%), Europe (25%) and Asia (23%) with only small fractions of reports coming from Latin America & Caribbean (4%), Oceania (2%), and Africa (2%).

Figure S2 in the online resource lists WHO PIDM member countries contributing at least 1% to all reports in VigiBase per product type. Countries with the largest individual contributions include seven long-standing members of the programme since its inception in 1968 (USA, Canada, UK, Germany, Netherlands, Australia, and New Zealand). China and South Korea are examples of Asian countries with large contributions to medicine reports (~8% each). According to the 2024 World Bank income classification groupings (see Supplementary Table 2 in the online resource), 18% of all VigiBase reports are from low- and middle-income countries (LMICs). Larger contributions from high-income countries can be explained by their broader access to medicines, greater resource base, and more mature infrastructure for pharmacovigilance monitoring [51, 52]. In contrast, LMICs often face challenges in developing and maintaining pharmacovigilance systems due to resource constraints, where trained human resources are often scarce and needed in other positions. Variations in demographics, disease patterns, and cultural norms may further explain the uneven report volumes between high-income and LMICs [53].

In terms of report type and source, 86% of all reports in the database are unsolicited (marked as 'spontaneous'

in E2B), with this proportion being higher for vaccine reports (96%). The remainder of reports mostly come from studies, including those conducted as part of post-marketing surveillance and special monitoring programmes. While it is mandatory for marketing authorisation holders (MAHs) to share (certain) reports with regulatory authorities in most countries, they also receive reports unsolicited from healthcare professionals (HCPs) or consumers. Half of all VigiBase reports come from MAHs, but their representation is lower in vaccine reports than in medicine reports.

In terms of reporter qualification, most cases are reported by HCPs [i.e., ~ 59% in total including reports from physicians (31%), pharmacists (10%) and other HCPs (18%)]. Additionally, a considerable number of reports (38%) come from consumers and non-HCPs, and for COVID-19 vaccines this category is the most common reporter qualification (55%).

Eighty-nine percent of all reports list only one suspected and/or interacting medicinal product (at active ingredient level), while 11% report between two and five, and a small fraction (0.5%) include more than five. Among non–COVID-19 vaccine reports, the proportion of reports with a single vaccine is lower (79%). More than 50% of all reports list more than one MedDRA® AE preferred term (PT), with this proportion being greater for vaccine reports. The seriousness of a report in VigiBase refers to the ICH seriousness criteria [54] and is harmonised at case level in line with the official E2B (R2) format. For cases reported in the R3 format, where seriousness is recorded at the event level, a case is considered serious if it contains at least one serious AE [24]. Overall, a greater proportion of medicine than vaccine reports are labelled as serious. Around six percent of all medicine reports indicate fatal or life-threatening outcomes, irrespective of the relationship of the outcomes with the suspected product. Of note, a relatively large number of both medicine and vaccine reports are categorised as other medically important conditions. Since this category is not defined by strict criteria, it allows for greater variability and may be interpreted differently depending on the reporter's expertise and judgement.

The availability of information on other selected structured fields used in assessments varies across the database. Time-to-onset (TTO) data are available for most vaccine reports (85%), but less so for medicine reports (53%). Among medicine reports, information on dose is available in approximately 40% of reports, while indication data are provided in about 65% of reports.

4 Trends in VigiBase Report Characteristics

This section describes trends in VigiBase over the past 10 years comparing reports submitted before (~10 million reports) and after (~24 million reports) 1 January 2015. The COVID-19 vaccine reports were excluded from these analyses as their overwhelming presence in recent years could obscure relevant trends in reporting patterns for medicines and other vaccines.

Over the years, an increase in geographic spread is observed (Fig. 4, and Fig. S3 in the online resource), reflecting the expansion of the programme (see online resource, Fig. S4). Since 2015, the most notable shift is the increasing proportion of reports from Asia (Fig. 4), accounting for 29% of all reports shared from 2015 onwards compared to 13% before. While report contributions from Latin America and the Caribbean, as well as Africa, have also increased more than two-fold since 2015, reports from these regions still make up relatively small portions of the database.

Another notable trend, broadly consistent across all regions, is the increasing contribution of reports submitted

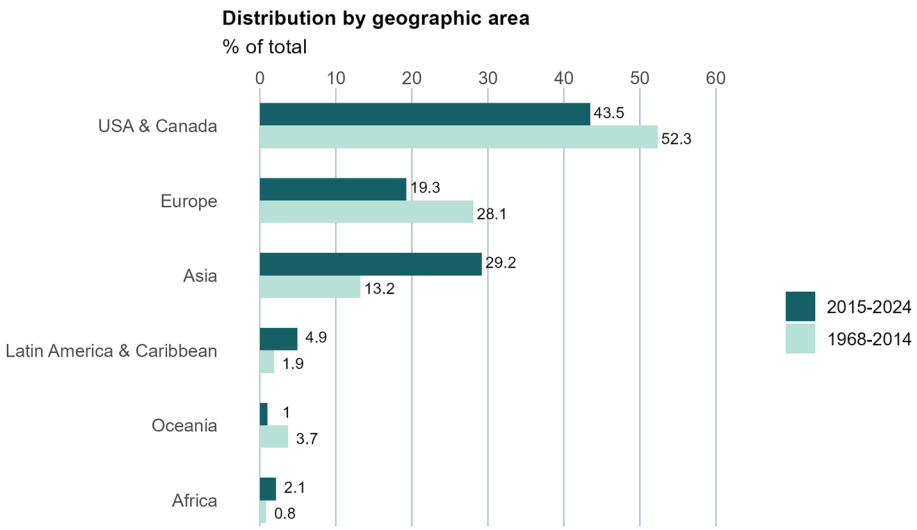

Fig. 4 Geographic distribution of reports: comparing reports received in 2015–2024 versus 1968–2014. For each calendar period, the percentages shown represent the relative contribution of each geographic area to the total reports with a suspected and/or interacting medicinal product. COVID-19 vaccine reports were not included in these analyses.

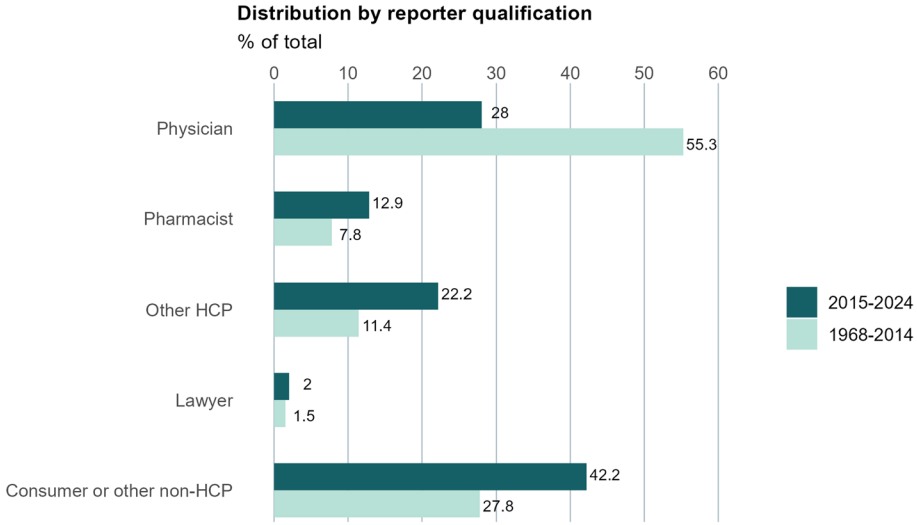

Fig. 5 Distribution by reporter qualification: comparing reports received in 2015–2024 versus 1968–2014. For each calendar period, the percentages shown represent the relative contribution of each reporter qualification to the total reports with a suspected and/or interacting medicinal product. Since reports with multiple reporter qualifications were assigned to each of the relevant qualifications, the total sum of the percentages exceeds 100%. COVID-19 vaccine reports were not included in these analyses. *HCP* Health Care Professional

by non-physician reporters, i.e., by pharmacists (13% vs 8%), other HCPs (22% vs 11%) and consumers and other non-HCPs (42% vs 28%) (Fig. 5, see also online resource, Figs S5 and S6). Overall, this trend reflects the growing number of countries sharing reports from these reporters over time (see online resource, Fig. S7), a change that is partly driven by legislation allowing and promoting direct patient reporting [55, 56] and enabling non-physician HCPs to serve as independent reporters [57–59]. In addition, the growing involvement of patients and patient organisations in pharmacovigilance networks [60, 61] as well as other initiatives to encourage reporting by pharmacists and nurses [62], may have contributed to this trend.

To identify key trends in medicinal product and AE reporting patterns before and after 1 January 2015, we used vigiPoint [43], UMC's method to pinpoint differences in relative frequencies across data subsets, accounting for absolute frequency and strength of association in a single statistical measure. Of note, trends observed in these analyses do not directly reflect changes in product safety profiles, as they are influenced by various factors including trends in usage patterns, regulatory guidance, awareness and/or implementation of electronic reporting tools. Moreover, any decline in relative share identified in these analyses may also reflect proportional shifts driven by increasing representations of other reports in the database, particularly when no specific driver of a trend can be identified.

Figure 6 summarises recent shifts in the distribution of reports by the suspected and/or interacting medicinal products, grouped by their mapped official ATC therapeutic subgroup (for completeness, we also provide the same figure based on both official and UMC-assigned ATC codes as Fig. S8 in the online resource). Across geographic regions, reports on antineoplastic and immunosuppressant drugs have become relatively more prominent, accounting for 11.6% and 14.2% of all reports in the database since 2015, respectively, compared to 6.3% and 9.0% prior to that. This trend is also seen across various reporters, with antineoplastics being increasingly reported by physicians as well as consumers and other non-HCPs, and immunosuppressants by both physicians and pharmacists (Fig. S9 in the online resource). Conversely, reports on products targeting cardiovascular, nervous, musculoskeletal and genitourinary systems have declined in relative share over the same period. Overall, these trends align with regulatory approval rates, reflecting the strong presence of anti-cancer and immunomodulatory drugs in recent drug development and expedited approvals, in contrast to the slower progress in approval for neurological disorders and cardiovascular conditions [63–65]. Of note, there are also some region-specific trends, such as the higher proportion of vaccine reports in Africa since 2015, which is likely a reflection of the increasing involvement of national immunisation programmes in the WHO PIDM, and the increasing access to vaccines in this region [66].

Figure 7 summarises recent patterns in the reporting of AEs, grouped by MedDRA® High Level Group Terms (HLGTs). Over the past decade, the most notable global trend is the marked increase in the percentage of reports on 'medication errors and other product use errors and issues' (more than 3-fold) and off-label uses and intentional product misuses/use issues' (5-fold), representing 8.7% and 3.0% of all reports in the database since 2015, respectively, compared with 2.5% and 0.6% before 2015. This trend is evident across a wide range of reporters (Fig. S10 in the online resource) and likely reflects the gradual incorporation of these concepts into regulatory frameworks under new pharmacovigilance legislation [67]. In several geographic areas, a rise in reports classified under the 'investigations' system organ class (SOC) is also observed. Furthermore, there has been an increased share of reports related to 'viral

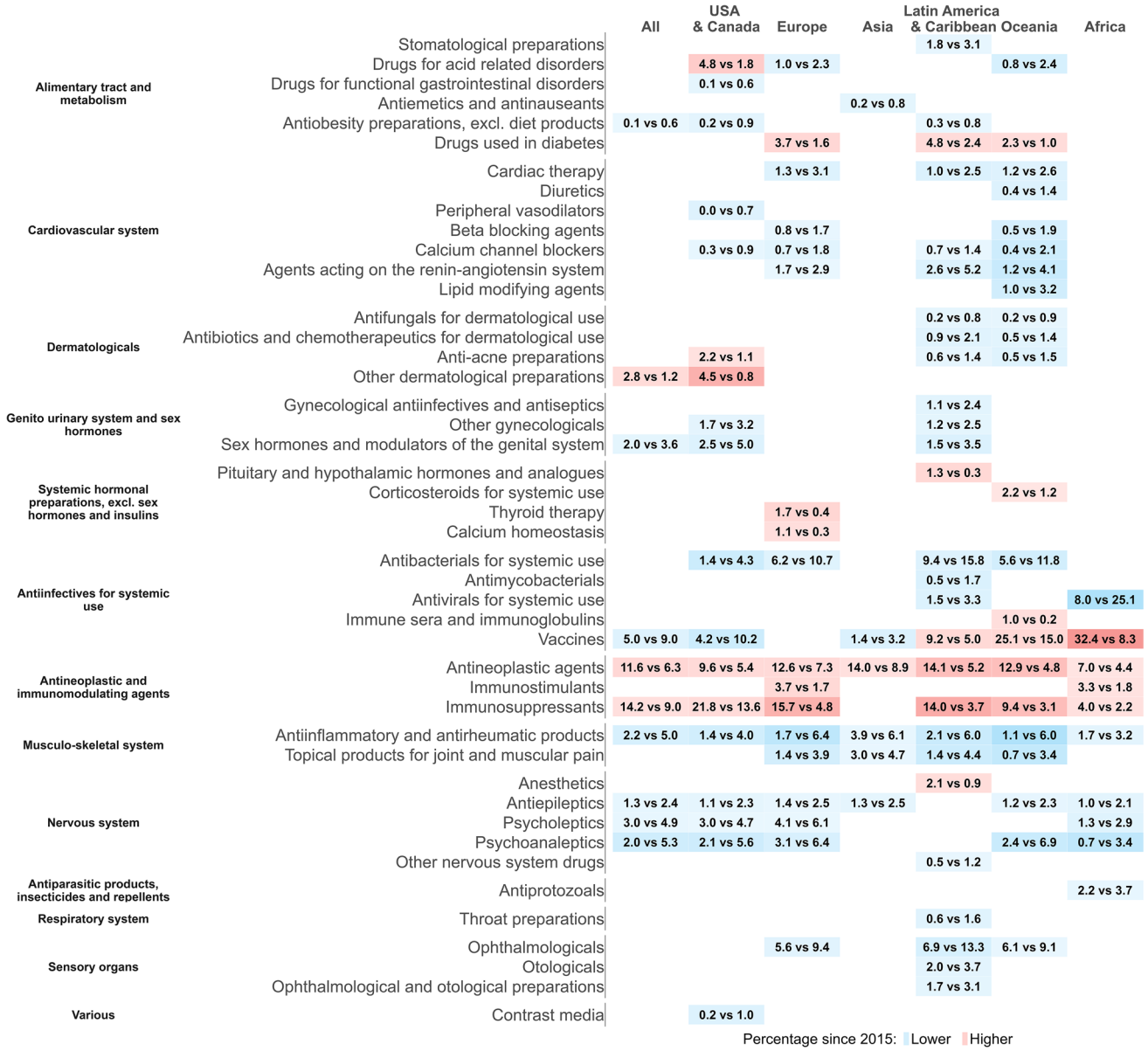

Fig. 6 Anatomical Therapeutic Chemical (ATC) therapeutic subgroups with a higher or lower relative representation in VigiBase since 2015, based on percentage distributions (2015–2024 vs 1968–2014), overall and by geographic area. Distribution of ATC (level 2) therapeutic subgroups for medicine and vaccine (non–COVID-19) reports with a higher (in red) or lower (in blue) relative representation in VigiBase since 2015 (a total of 45 terms), overall and by geographic area. ATC therapeutic subgroup terms are grouped by ATC (level 1) anatomical group. Each cell summarises the percentage of all reports with the ATC therapeutic subgroup listed for the period 2015–2024 compared to the corresponding percentage in the period prior (1968–2014). Of note, some medicinal product active ingredients map to more than 1 ATC level 2 term since several therapeutic subgroups may include the same active ingredient when used in different therapeutic indications, formulations or routes of administration (e.g., corticosteroids) This replication can result in the repetition of patterns across ATC level 2 terms

infection disorders,' other types of infections, and 'therapeutic and nontherapeutic effects (excluding toxicity)' since 2015. These shifts are primarily driven by the surge in reports related to COVID-19, other respiratory infections, and SARS-Cov-2 tests during the pandemic period. Another cross-regional trend is the greater relative representation of reports on 'device issues', partly attributable to concerns surrounding levonorgestrel-releasing intrauterine devices (IUDs) [68], which emerged in Europe around 2017. Regulatory changes including amendments to EU medical device legislation introducing mandatory reporting [69] and the launch of the FDA's Voluntary Malfunction Summary Reporting programme launched to improve the safety monitoring of devices [70] may also have contributed to

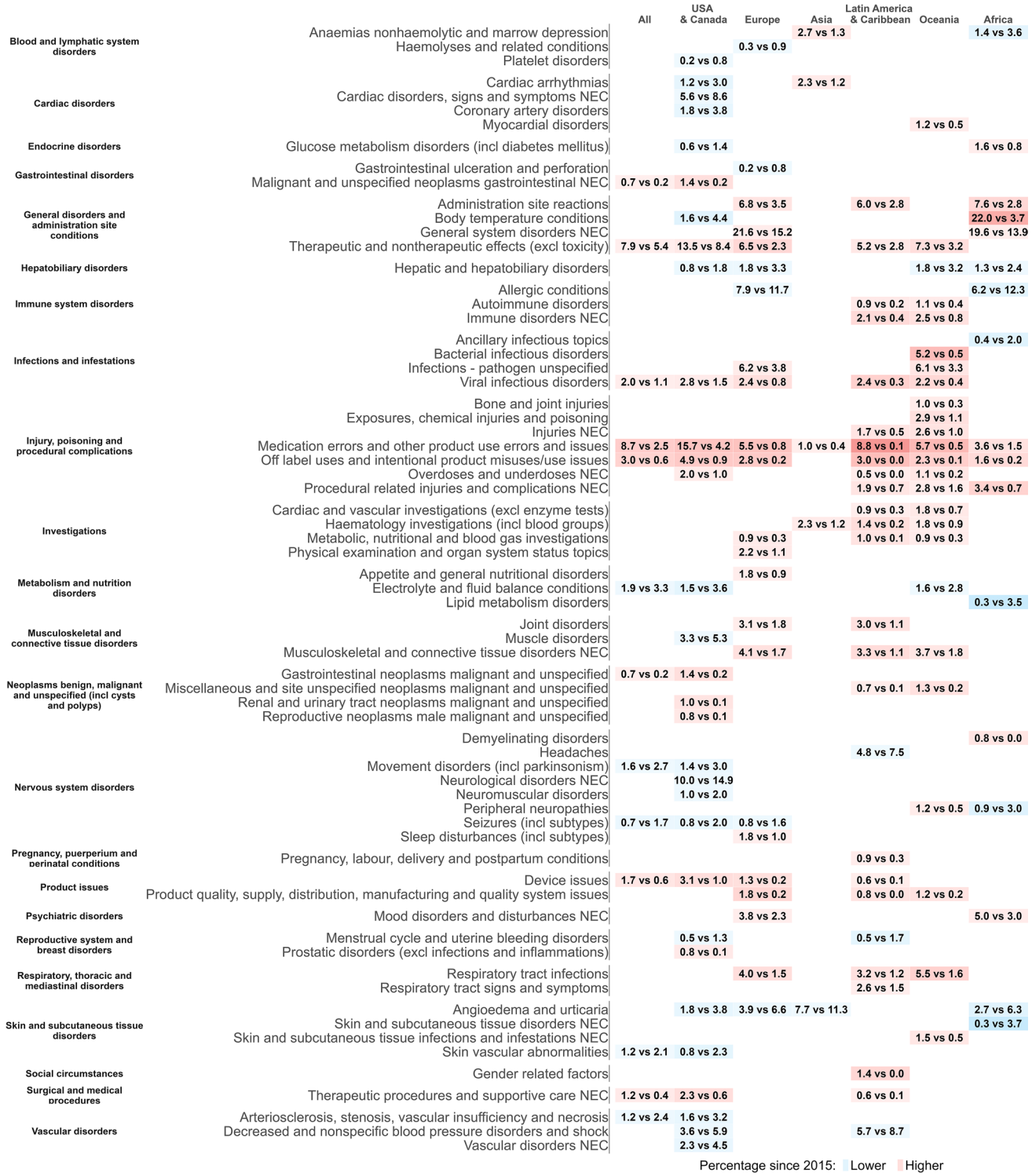

Fig. 7 MedDRA® High Level Group Terms (HLGTs) higher or lower-errelative representation in VigiBase since 2015, based on percentage distributions(2015–2024 vs 1968–2014), overall and by geographic area. Distribution of HLGTs for medicine and vaccine (non–COVID-19) reports with a higher (in red) or lower (in blue) relative representation in VigiBase since 2015 (a total of 68 terms), overall and by geographic area. HLGTs are grouped by system organ class (SOC). Each cell summarises the percentage of all reports with the HLGT listed for the period 2015–2024 compared to the corresponding percentage in the period prior (1968–2014). *NEC* not elsewhere classified

this trend. Conversely, terms mapped to the SOCs 'cardiac disorders,' 'vascular disorders,' 'nervous system disorders' and 'skin and subcutaneous tissue disorders' have declined. Examples of these HLGTs are those related to arrhythmias, hypotension, parkinsonism, and urticaria. These conditions have long been recognised as typical adverse drug reactions and historically accounted for a significant share of reports. While they remain clinically relevant and still contribute a significant portion of reports in VigiBase, their relative representation has diminished over time due to the growing contribution of reports concerning other event categories.

5 Strengths and Limitations of the Database

VigiBase enables global exploration and analysis of reports of AEs for medicines and vaccines collected by WHO PIDM member organisations in more than 160 countries around the world, supporting signal management and methodological research. VigiBase may also serve as a complement to other sources of evidence for-in depth analysis of signals and problems related to the use of medicinal products [71]. Like other surveillance systems based on individual case reports, VigiBase benefits from continual data collection, a broad coverage of medicinal products and AEs, and the capability to, at least in principle, collect detailed information in an efficient way. The uniquely broad scope of the data, reflecting diverse patterns of medicinal product use and indications, also offers valuable insights into off-label use, traditional medicines and combinations therapies, which are often not well captured in other data sources. The increasing diversity of reporters further adds to the breadth and depth of information available in VigiBase. Health care professionals typically report issues that occur during patient care including serious events requiring intervention and safety issues related to dosage and/or interactions. Patients, on the other hand, tend to provide more detailed information on the specific circumstances, severity and impact of the AE [72–74]. Patients also play an important role in reporting AEs linked to specific products such as herbal and over-the-counter medicines as well as product-related issues that might otherwise go unnoticed [73].

A key advantage of a global database like VigiBase is its size, which allows for the analysis of small subgroups and rare events that may not be captured or remain unnoticed in national or regional databases. It also serves as a valuable resource for member organisations in countries with low reporting rates and low resource settings, as access to international data can support smart, cost-efficient local policies in pharmacovigilance that promote reliance on the global data for broad insights, with focused/prioritised safety monitoring of medicinal products that are exclusive to these settings [75]. The global nature of VigiBase further offers unique opportunities for cross-country and regional comparisons. For example, consistent reporting patterns across countries could strengthen the plausibility of a signal, as these patterns are less likely the result of chance or country-specific biases. However, as with any signal, causality assessments require a thorough evaluation of all available evidence and, ideally, complementary analyses using data sources that are better suited to address the inherent biases of case reports, especially when such biases extend across multiple countries or regions. In this context, it is important to note that, although VigiBase has become geographically more diverse in recent years, most reports still come from Western high-income areas (including the USA and Europe). The geographic distribution of reports therefore underscores the need of ongoing efforts to broaden VigiBase's global coverage, also to better capture products and events that are more common in LMICs [76, 77].

The heterogeneity of the data captured by VigiBase also represents one of its key limitations. Geographical differences in product use, healthcare access, and data collection (including reporting and coding practices) can make the interpretation of global data more challenging, even more so when such practices change over time. Likewise, different channels for report entry (resulting in multiple copies entering the database from different sources) and country-level variation in legislation (defining who can report, data protection laws and the periodicity of data sharing) add another level of complexity when assessing AE patterns in real time [78]. Therefore, subgroup-specific analyses, such as by geographic region or country, should always be considered. In addition, reporting formats and terminologies can vary, although there have been continual efforts toward data harmonisation, including the incorporation and use of WHO-ART, MedDRA®, and WHODrug terminologies [79] and the E2B format for report transmission. Lastly, the quality of data in terms of completeness, data accuracy and potential misclassification naturally varies more in a global repository, as do the requirements for submitting cases in terms of level of suspected causality. Due to the greater distance to the reporter, it is difficult to influence the quality and timeliness of the data, which can make signal management activities in a global context challenging. All these sources of variation require more advanced techniques for processing the data (e.g., when identifying duplicate reports) and metadata documentation (including quality metrics, such as vigiGrade [43]) to mitigate biases and misinterpretations when analysing and interpreting the data. At the same time, the heterogeneity of the data underscores the importance of ongoing efforts to harmonise reporting practices and improve data quality and report completeness at the source. Problems associated with completeness of data elements relevant for causality assessment have been repeatedly

demonstrated in various settings [80, 81]. This has resulted in the development of completeness scores that pinpoint essential missing information requiring awareness among reporters and guiding signal assessors in the prioritisation of reports for analysis. Beyond this, more structural and organisational measures are needed as improving report completeness ultimately relies on multiple factors, including robust quality management systems, pharmacovigilance staffing, integration of electronic reporting within healthcare workflows, training healthcare personnel, and fostering inter-professional collaboration [82, 83]. In terms of further data harmonisation, the Identification of Medical Products (IDMP) developed by the Organization for Standardization (ISO) [84] may provide opportunities to capture more rich and precise information on medicinal products, including route of administration and strength. Likewise, future automated processing of free text data (using artificial intelligence) may help to make this information more readily accessible, including data recorded in different languages at the source.

6 Conclusions

VigiBase has expanded not only in size but also in scope, with greater contributions from geographic areas and reporters that were less represented 10 years ago. Knowledge of these patterns as well as methods and tools to analyse the data will provide context to users of VigiBase and the global pharmacovigilance community. Because of its coverage and scale, VigiBase is a valuable source for scientific development and signal management, as well an important source of global reference and reliance in pharmacovigilance provided that the data are properly analysed and interpreted considering its strengths and limitations.

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Declarations

Conflict of Interest JSB, OG, DS, MF, HS, TB, LS, MW, and PH have no conflict of interest to declare. GNN is an Editorial Board member of *Drug Safety*. GNN was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Availability of Data and Material The data that support the findings of this study are not publicly available. Access to the data is restricted based on the conditions for access within the WHO Programme for International Drug Monitoring. Subject to these conditions, data are available from the authors on reasonable request. For further inquiries, please contact Uppsala Monitoring Centre via https://who-umc.org/contact-information/.

Consent to Participate Not applicable.

Ethical Approval Not applicable.

Author Contributions JSB, OG, DS, and GNN were responsible for the conceptualisation of this work. JSB performed the formal analysis of the data. All authors participated in interpreting the results from the data. JSB drafted the manuscript with support from OG, DS and GNN. All authors reviewed and edited the manuscript and approved the final version for submission.

Consent for Publication Not applicable.

Code Availability The code used to analyse the reports from VigiBase will be made available on reasonable request.

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