European Journal of Clinical Pharmacology (2025) 81:1287–1299
https://doi.org/10.1007/s00228-025-03862-2

RESEARCH

Trends in adverse drug reaction reporting in eight selected countries after the implementation of new pharmacovigilance regulation in 2012: a joinpoint regression analysis

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Received: 22 October 2024 / Accepted: 2 June 2025 / Published online: 17 June 2025

Abstract

Background and purpose Underreporting of adverse drug reactions (ADRs) remains to be a challenge in modern health care. Major reforms in the EU pharmacovigilance system in 2012 introduced the legal basis for consumers to report suspected ADRs. This study was designed to determine trends in overall ADR reporting, the ratio of health care professional (HCP)-to-consumer ADR reporting, and the ratio of serious-to-nonserious ADR reporting for an 11-year period in the selected non-EU and EU countries that had implemented systems for consumers' reporting before the 2012 EU pharmacovigilance legislation and those that did not have.

Materials and methods The national competent authorities of 15 countries (11 EU countries, former EU member the UK, Australia, Canada, and the USA) were contacted via e-mail and asked to provide the total number of ADR reports, numbers of ADRs reported by consumers and HCPs, numbers of serious and nonserious ADRs, and top 5 medication groups causing ADRs by the Anatomical Therapeutic Chemical (ATC) classification system during the period of 2012–2022. Eight countries, namely Belgium, Canada, Finland, Lithuania, the Netherlands, Portugal, Sweden, and the UK, responded and provided the data. The trends of ADR reporting were evaluated with the joinpoint regression analysis method. The annual percent change (APC) and the average annual percent change (AAPC) were estimated.

Results Over the study period, the overall rates of ADR reporting increased significantly in all the countries except for Belgium, with the greatest AAPC being in Lithuania (AAPC of 32.34) and the lowest, in Canada (AAPC of 10.3). The ratios of HCP-to-consumer ADR reporting were significantly decreasing in all the countries (AAPC range, –43.7 to –24.9) except for Canada where an opposite significant trend toward an increasing HCP reporting rate (AAPC of 3.9) for 2012–2020 was observed. The ratios of serious-to-nonserious ADR reporting were significantly decreasing in more than half of the countries, namely Canada, Finland, Lithuania, the Netherlands, and Portugal, with the greatest negative AAPC being in Lithuania (AAPC of –32.9) and the smallest, in Canada (AAPC of –6.8). Vaccines (J07), immunosuppressants (L04), antineoplastic agents (L01), antibacterials for systemic use (J01), and antithrombotic agents (B01) were found to be the top 5 most frequently reported medications.

Conclusions This study shows the significant upward trends in overall ADR reporting not only in the countries that implemented consumer ADR reporting systems after the 2012 EU pharmacovigilance legislation but also in countries that had consumer reporting systems before 2012. Moreover, significant downward trends in the ratios of HCP-to-consumer ADR reporting were documented for all EU countries, confirming increasing consumers' involvement in ADR reporting. Further, larger scale studies with the involvement of more countries are needed to better understand the trends in ADR reporting, and multifaceted interventions are warranted to be installed to enhance ADR reporting.

Keywords Adverse drug reactions · Consumers · Health care professionals · Anatomical Therapeutic Chemical classification system · Joinpoint regression analysis

Introduction

Across the world, adverse drug reactions (ADRs) remain a huge burden to health care, leading to significant morbidity, mortality [1], and costs [2]. The World Health Organization

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(WHO) defines an ADR as "a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [3]. The data show that approximately 5% of all the hospitalizations are due to ADRs [4], and the incidence of fatal ADRs ranges from 0.2% to 0.5% [5–7]. ADRs are considered one of the top 10 causes of all deaths in the developed world [8]. A meta-analysis by Lazarou et al. in 1998 concluded that ADRs might rank from the fourth to sixth leading cause of death in the USA [5]. It is estimated that the annual costs of ADRs are more than $13 billion in Canada [9], $30 billion in the USA [10], $460 million in Australia [11], and £2.2 billion in the UK [12].

Traditionally, health care professionals (HCPs) have been considered a key source of spontaneous ADR reporting [13]. However, underreporting is a well-recognized issue not only among HCPs [14, 15] but also among patients [17, 18]. Organizations such as the WHO and the European Union (EU) have acknowledged the potential and value of patient reporting and have laid a sound foundation for major reforms in the EU pharmacovigilance system that took place in 2012 in the EU countries, including Lithuania. The introduction of the legal basis for the patient to report ADRs to national competent authorities was one of these major changes [16]. The new EU pharmacovigilance legislation mandated EU countries to encourage patient reporting directly to national competent authorities through awareness-raising activities and strengthening patients' knowledge about pharmacovigilance, as well as to enable ADR reporting through easy and effective reporting mechanisms such as direct online reporting [17]. Furthermore, the new reporting rules enabled the provision of instructions on ADR reporting in drug package leaflets and labelling medicines that are being monitored particularly closely with a black inverted triangle to address the need for enhanced reporting [19, 20]. Even after 18 months of this legislation being operational, positive results in patient safety and an overall increase in ADR reports by consumers were observed [19].

Since then, many studies have clearly shown considerable patients' contributions to spontaneous ADR reporting [16, 20–22]. However, to the best of our knowledge, no study investigating the trends in reporting ADRs by consumers and HCPs within the period after 2012 has been carried out to date. Therefore, the aim of this study was to determine trends in overall ADR reporting, the ratio of HCP-to-consumer ADR reporting, and the ratio of serious-to-nonserious ADR reporting for an 11-year period in the selected non-EU and EU countries that had implemented systems for consumers' reporting before the 2012 EU pharmacovigilance legislation and those that did not have. Moreover, we aimed to identify the most frequently reported medications causing ADRs.

Materials and methods

Study design

This study was carried out from February 2023 to March 2024. A questionnaire along with the study purpose was sent to the national competent authorities of the selected countries via e-mail. The selected countries ($n = 15$) included several non-EU countries and the member states of the EU that had established systems for ADR reporting by patients before 2012 (Australia, Canada, the USA, the UK (now former EU country), the Netherlands, Denmark, France, Italy, and Sweden) as well as some EU countries where patient reporting became available after the adoption of the new EU pharmacovigilance legislation (Portugal, Finland, Belgium, Estonia, Latvia, and Lithuania). The contact information was taken from the official websites of the national competent authorities. If the response was not received, the questionnaire was resent repeatedly within the period of 4–8 weeks. Of the 15 countries selected, the national competent authorities of 8 countries, namely Belgium, Canada, Finland, Lithuania, the Netherlands, Portugal, Sweden, and the UK, answered and provided the information requested. For Canada, the data related to COVID-19 vaccination were additionally collected from the Canadian Adverse Events Following Immunization Surveillance System webpage [23]. The 4-item questionnaire asked to provide the following data by year for the period from 2012 until 2022: the total number of ADR reports, the numbers of ADRs reported separately by HCPs and consumers, the numbers of serious and non-serious ADRs, and top 5 medication groups causing ADRs by the Anatomical Therapeutic Chemical (ATC) classification system [24]. This system classifies active substances in a hierarchical manner with five different levels. There are 14 main anatomical/pharmacological groups that are further divided into the 2nd level (pharmacological or therapeutic subgroup), 3rd and 4th levels (chemical, pharmacological, or therapeutic subgroup), and 5th level (chemical substance) [24]. We analyzed top 5 medication groups causing ADRs by the 2nd level (therapeutic subgroup).

HCPs were considered individuals licensed, registered, or certified under the laws or regulations of a particular country to provide health care services (physicians, pharmacists, and nurses). Consumers were defined as individuals that were not HCPs (patients or their relatives). A serious ADR was defined as an adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or causes a congenital abnormality/birth defect [25].

Data analysis

The overall numbers of ADRs were converted to incidence rates per 100,000 population using the data on the total population obtained from the national statistics authorities of each selected country. The ratios of HCP-to-consumer ADR reporting and the ratios of serious-to-nonserious ADR reporting were calculated for each country by year.

The Joinpoint Regression Program version 5.0 (Division of Cancer Control and Population Sciences, National Cancer Institute, Information Management Services, Inc., Calverton, MD) was used to perform the analysis of trends. We used ADR reporting rates, the ratio of HCP-to-consumer ADR reporting, and the ratio of serious-to-nonserious ADR reporting as inputs. The join point regression models employ joined linear segments on a logarithmic scale to define the year(s) when significant changes in trends occurred, i.e., identifies the periods that can be separated by inflection points, so-called joinpoints, and determines the pattern of a trend (upward, downward, or stationery). The number of joinpoints is obtained using permutation tests via Monte Carlo resampling. For the number of data points between 7 and 11, only one join point is available (in our study, we analyzed data for the 11-year period). Which model is better—with one or no joinpoint—is determined based on the Weighted Bayesian Information Criterion (WBIC). The model with a smaller WBIC is better.

Once the line segments have been established, the estimated annual percent change (APC) is used to describe the magnitude and direction of trends in the ADR reporting rate, ratio of HCP-to-consumer ADR reporting, or ratio of serious-to-nonserious ADR reporting. Testing the hypothesis (two-sided p value = 0.05) that the APC is equal to zero is equivalent to testing the hypothesis that the trend is neither increasing nor decreasing. To compare trends over the whole period, the average annual percent change (AAPC) is estimated. When there are no joinpoints, the APC is constant and equals the AAPC. The 95% confidence intervals (95% CI) for APC and AAPC were calculated using the parametric method. The APC or the AAPC is statistically significant when its 95% CI does not include zero.

For the evaluation of the most common medications causing ADRs over the study period in each country, we determined the top 5 most frequently reported medication groups classified according to the ATC classification system (ATC second level). The data on the therapeutic groups according to the ATC system were ranked as follows: the first place, the second place, and so on. The rank information was converted into a numerical format based on a 5-point scale: the first place got 5 points, while the fifth place got 1 point. If any therapeutic subgroup did not appear in the top 5 in a particular year, no points were given. The points over the whole period were added up to obtain a total score based on which the top 5 most frequently reported therapeutic subgroups were identified for each country. Later, we determined the top 10 most frequently reported therapeutic subgroups by the total score across all countries. The stability of ranks over the years for each country was tested by Friedman's test; differences in the distributions of ranks were not significant if $p > 0.05$.

Data analysis was carried out using MS Excel and SPSS version 29 programs.

Results

Overall trends in ADR reporting in eight countries, 2012–2022

Trends in ADR reporting in eight selected countries during the study period of 2012–2022 are shown in Table 1 and Fig. 1 (incidence rates per 100,000 population for each country are shown in Supplementary Table 1). The analysis revealed that ADR reporting rates during the 11-year period increased significantly in all the countries except for Belgium. The greatest AAPC was observed for Lithuania (32.34; 95% CI, 16.8 to 50.0), followed by the Netherlands (24.2; 95% CI, 6.8 to 44.5) and the UK (22.9; 95% CI, 5.6 to 43.0), while the lowest was in Canada (10.3; 95% CI, 7.4 to 13.3).

One joinpoint was identified only in Belgium in 2019. However, in Belgium, an upward trend for both periods was insignificant ($APC_{2012–2019}$ = 6.5; 95% CI, − 29.7 to 61.3) and $APC_{2019–2022}$ = 164.0; 95% CI, − 44.2 to 1149.7). In other countries, the joinpoint regression analysis showed no join point; therefore, the APC is the same as the AAPC.

Changes in the ratio of ADRs reported by HCPs and consumers, 2012–2022

During the study period, the ratios of HCP-to-consumer ADR reporting were significantly decreasing in all the countries (AAPC range, − 43.7 to − 24.9) except for Canada where an opposite significant trend toward an increasing HCP reporting rate (AAPC of 3.9; 95% CI, 0.5 to 7.4) was observed for 2012–2020 (Table 2, Fig. 2, and Supplementary Table 2). The greatest negative AAPC was documented for Lithuania (− 43.7; 95% CI, − 60.4 to − 19.9) followed by Finland (− 34.1; 95% CI, − 43.7 to − 22.9) and Belgium (− 32.4; 95% CI, − 38.3 to − 25.9).

The analysis found no joinpoints for Belgium and Canada, indicating stationary trends in the ratios of HCP-to-consumer ADR reporting over the study period in these countries. Regarding changes in trends in the one-joinpoint countries, joinpoints toward an accelerated decrease in the ratios, indicating increased reporting rates by consumers, were observed for Finland in 2020, Sweden in 2019, and

Table 1 Trends in adverse drug reaction reporting in eight countries, 2012–2022

Country	Period	APC (95% CI)	AAPC (95% CI)
Non-EU and EU countries having consumer reporting systems before 2012			
Canada	2012–2022	10.3* (7.4; 13.3)	10.3* (7.4; 13.3)
UK	2012–2022	22.9* (5.6; 43.0)	22.9* (5.6; 43.0)
Netherlands	2012–2022	24.2* (6.8; 44.5)	24.2* (6.8; 44.5)
Sweden	2012–2022	15.7* (0.9; 32.6)	15.7* (0.9; 32.6)
EU countries that implemented consumer ADR reporting systems after 2012			
Belgium	2012–2019	6.5 (− 29.7; 61.3)	39.8 (− 10.0; 117.1)
	2019–2022	164.0 (− 44.2; 1149.7)	
Finland	2012–2022	15.4* (1.8; 31.0)	15.4* (1.8; 31.0)
Lithuania	2012–2022	32.34* (16.8; 50.0)	32.34* (16.8; 50.0)
Portugal	2012–2022	18.0* (7.3; 29.9)	18.0* (7.3; 29.9)

APC annual percent change, *AAPC* average annual percent change

*Indicates that the APC or the AAPC is significantly different from zero ($p < 0.05$)

the Netherlands in 2020. For Lithuania and Portugal, a joinpoint toward an accelerated increase in the ratios was recorded in 2014 for both countries, but it is worth noting that the APCs for the period of 2012–2014 were not statistically significant for both countries as well.

Changes in the ratio of serious-to-nonserious ADR reporting, 2012–2022

During the study period, the ratios of serious-to-nonserious ADR reporting were significantly decreasing in more than half of the countries, namely Canada, Finland, Lithuania, the Netherlands, and Portugal (Table 3, Fig. 3, and Supplementary Table 3). The greatest negative AAPC was documented for Lithuania (− 32.9; 95% CI, − 38.4 to − 26.9), and the smallest for Canada (− 6.8; 95% CI, − 9.9 to − 3.7). Despite the AAPC for Belgium not being significant, analysis found a joinpoint in 2019 showing a significant downward trend for 2012–2019 (APC = − 11.8; 95% CI, − 17.4 to − 5.7) and a significant upward trend for 2019–2022 (APC = 22.9; 95% CI, 8.6 to 39.2). Neither the APCs nor the AAPC were found to be significant for Sweden and the UK.

The most frequently reported drugs causing adverse drug reactions

In this part of our study, we evaluated data from seven countries. Table 4 shows the top 5 most frequently reported drug groups classified according to the ATC classification system. Unfortunately, we could not include the data from Belgium as no information on this was provided.

The top 5 most frequently reported ATC drug groups did not differ statistically significantly in every country over the study period. Vaccines (J07) were the most frequently reported ATC group in four countries, namely Finland, the Netherlands, Sweden and the UK. In Lithuanian, they ranked second, and in Portugal, fourth. Meanwhile, in Canada, they were not found to be present among the top 5 most common.

Immunosuppressants (L04) were the most frequently reported ATC group in Canada; in Portugal, second; in Sweden and the Netherlands, fourth; and in Finland and Lithuania, fifth. Antineoplastic agents (L01) ranked first in Portugal and Lithuania and second in Canada. In the Netherlands,

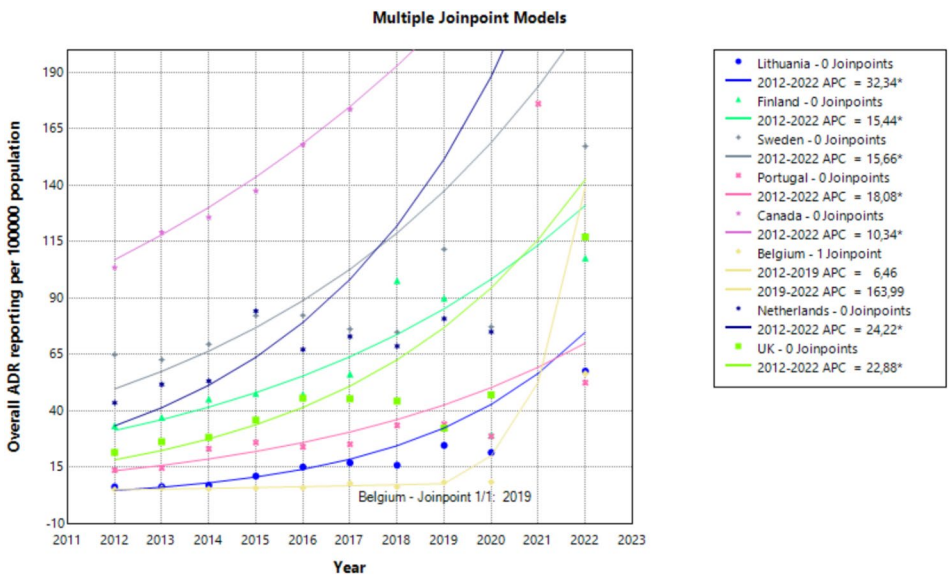

Fig. 1 Trends in adverse drug reaction reporting in eight countries, 2012–2022. The dots represent the values for a particular year. Trends are depicted with a regression line. To better visualize a separate trend for each country, the extreme values (related to the years of the COVID-19 pandemic) are not shown by shortening the scale on the *y* axis. *Indicates that the APC is significantly different from zero ($p < 0.05$)

Table 2 Trends in the ratio of adverse drug reactions reported by health care professionals and consumers in eight countries, 2012–2022[a]

Country	Period	APC (95% CI)	AAPC (95% CI)
Non-EU and EU countries having consumer reporting systems before 2012			
Canada[a]	2012–2020	3.9* (0.5; 7.4)	3.9* (0.5; 7.4)
UK	2012–2019	− 11.1 (− 30.2; 13.3)	− 24.9* (− 41.8; − 2.9)
	2019–2022	− 49.3 (− 79.5; 25.3)	
Netherlands	2012–2020	− 15.7* (− 19.7; − 11.4)	− 31.3* (− 36.2; − 25.6)
	2020–2022	− 69.7* (− 80.7; − 52.3)	
Sweden	2012–2019	− 8.2 (− 20.9; 6.6)	− 25.3* (− 36.2; − 12.5)
	2019–2022	− 53.8* (− 73.5; − 19.3)	
EU countries that implemented consumer ADR reporting systems after 2012			
Belgium	2012–2022	− 32.4* (− 38.3; − 25.9)	− 32.4* (− 38.3; − 25.9)
Finland	2012–2020	− 19.6* (− 27.1; − 11.4)	− 34.1* (− 43.7; − 22.9)
	2020–2022	− 70.2* (− 87.9; − 26.9)	
Lithuania	2012–2014	− 82.4 (− 97.7; 32.9)	− 43.7* (− 60.4; − 19.9)
	2014–2022	− 24.7* (− 39.6; − 6.2)	
Portugal	2012–2014	− 61.2 (− 88.5; 30.8)	− 27.2* (− 41.1; − 10.0)
	2014–2022	− 14.8* (− 25.4; − 2.8)	

APC annual percent change, *AAPC* average annual percent change

*Indicates that the APC or the AAPC is significantly different from zero ($p < 0.05$)

[a]The trend for Canada was calculated for the period of 2012–2020 due to missing data for 2021 and 2022

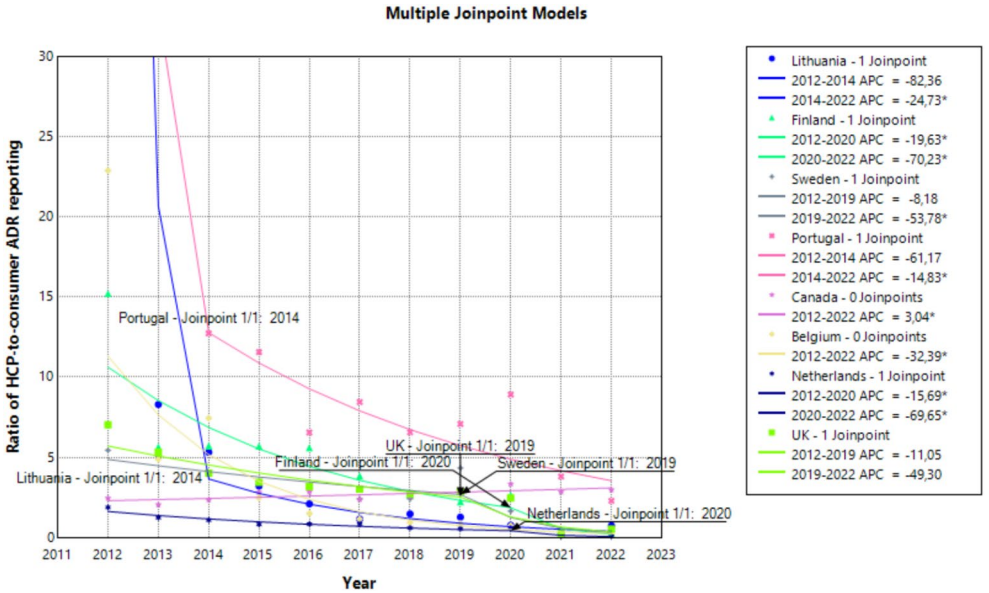

Fig. 2 Trends in the ratio of adverse drug reactions reported by health care professionals and consumers in eight countries, 2012–2022[a]. The dots represent the values for a particular year. Trends are depicted with a regression line. To better visualize a separate trend for each country, the extreme values (related to the years of the COVID-19 pandemic) are not shown by shortening the scale on the y axis. *Indicates that the APC is significantly different from zero ($p < 0.05$). [a]The trend for Canada was calculated for the period of 2012–2020 due to missing data for 2021 and 2022

Finland, Sweden, and the UK, these drugs were not among the top 5 most frequently reported therapeutic groups.

Psycholeptics (N05) ranked third in Canada, Finland, and Lithuania; in the Netherlands, Portugal, Sweden, and the UK, they were not among the top 5 most frequently reported therapeutic groups. Antithrombotic agents (B01) ranked second in Sweden; in the UK, third; in Finland and Lithuania, fourth; in the Netherlands, fifth; and in the remaining countries, they were not among the top 5 most frequently reported therapeutic groups.

Table 3 Trends in the ratio of serious-to-nonserious adverse drug reaction reporting in eight countries, 2012–2022

Country	Period	APC (95% CI)	AAPC (95% CI)
Non-EU and EU countries having consumer reporting systems before 2012			
Canada	2012–2022	− 6.8* (− 9.9; − 3.7)	− 6.8* (− 9.9; − 3.7)
UK	2012–2022	− 3.4 (− 10.9; 20.0)	− 3.4 (− 10.9; 20.0)
Netherlands	2012–2022	− 16.4* (− 22.2; − 10.2)	− 16.4* (− 22.2; − 10.2)
Sweden	2012–2022	− 10.2 (− 19.4; 0.1)	− 10.2 (− 19.4; 0.1)
EU countries that implemented consumer ADR reporting systems after 2012			
Belgium	2012–2019	− 11.8* (− 17.4; − 5.7)	0.7 (− 4.3; 6.0)
	2019–2022	22.9* (8.6; 39.2)	
Finland	2012–2019	− 26.4* (− 35.8; − 15.7)	− 18.5* (− 29.4; − 5.9)
	2019–2022	3.5 (− 37.7; 72.0)	
Lithuania	2012–2022	− 32.9* (− 38.4; − 26.9)	− 32.9* (− 38.4; − 26.9)
Portugal	2012–2022	− 16.7* (− 26.1; − 6.2)	− 16.7* (− 26.1; − 6.2)

APC annual percent change, *AAPC* average annual percent change

*Indicates that the APC or the AAPC is significantly different from zero ($p < 0.05$)

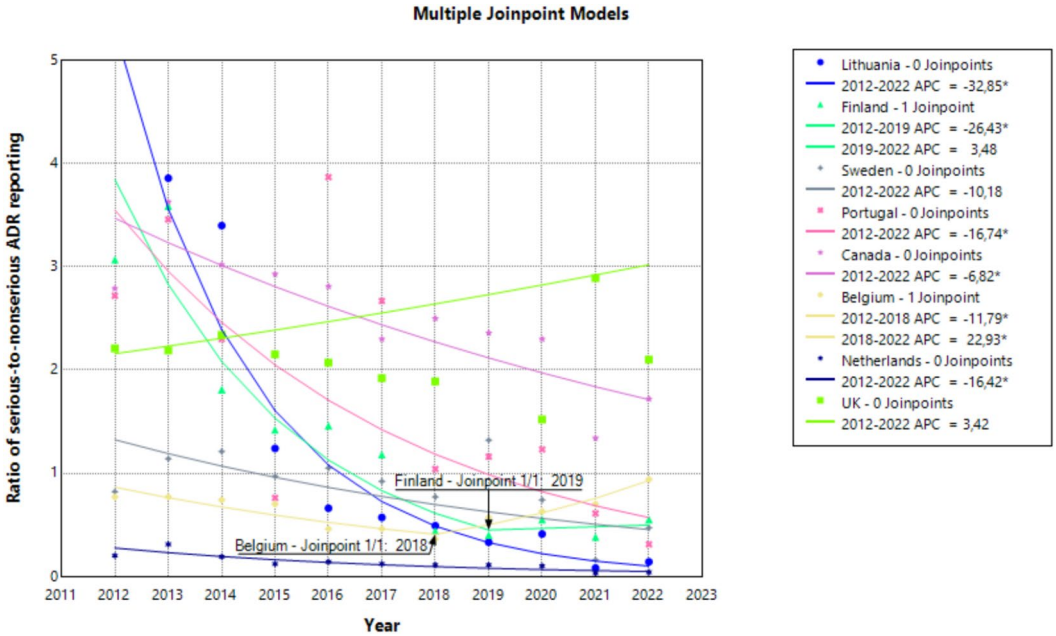

Fig. 3 Trends in the ratio of serious-to-nonserious adverse drug reaction reporting in eight countries, 2012–2022. The dots represent the values for a particular year. Trends are depicted with a regression line. To better visualize a separate trend for each country, the extreme values (related to the years of the COVID-19 pandemic) are not shown by shortening the scale on the *y* axis. *Indicates that the APC is significantly different from zero ($p < 0.05$)

Antibacterials for systemic use (J01) ranked second in the Netherlands and the UK and third in Portugal. Other gynecologicals (G02) were among the top 5 most frequently reported therapeutic groups only in two countries: Finland (second place) and Sweden (third place).

The top 10 most frequently reported therapeutic groups by the total score across all countries are displayed in Table 5. Vaccines (J07) ranked first, followed by immunosuppressants (L04), antineoplastic agents (L01), antibacterials for systemic use (J01), and antithrombotic agents (B01).

Discussion

Our study showed that the rates of overall ADR reporting during the 11-year period increased significantly in all the countries except for Belgium, with the greatest AAPC being in Lithuania and the lowest in Canada. While comparing the

Table 4 The top 5 most frequently reported therapeutic subgroups (ATC second level) by the total score in seven selected countries (excluding Belgium)

Country	TOP rank	ATC therapeutic subgroup	Total score[a]
Canada	1	Immunosuppressants (L04)	54
	2	Antineoplastic agents (L01)	42
	3	Psycholeptics (N05)	16
	4	Analgesics (N02)	15
	5	Drugs for obstructive airway diseases (R03)	15
Finland	1	Vaccines (J07)	54
	2	Other gynecologicals (G02)	29
	3	Psycholeptics (N05)	21
	4	Antithrombotic agents (B01)	20
	5	Immunosuppressants (L04)	12
Lithuania[b]	1	Antineoplastic agents (L01)	35
	2	Vaccines (J07)	34
	3	Psycholeptics (N05)	16
	4	Antithrombotic agents (B01)	8
	5	Immunosuppressants (L04)	7
Netherlands	1	Vaccines (J07)	54
	2	Antibacterials for systemic use (J01)	35
	3	Psychoanaleptics (N06)	30
	4	Immunosuppressants (L04)	18
	5	Antithrombotic agents (B01)	6
Portugal	1	Antineoplastic agents (L01)	48
	2	Immunosuppressants (L04)	42
	3	Antibacterials for systemic use (J01)	28
	4	Vaccines (J07)	26
	5	Antivirals for systemic use (J05)	17
Sweden	1	Vaccines (J07)	48
	2	Antithrombotic agents (B01)	33
	3	Other gynecologicals (G02)	21
	4	Immunosuppressants (L04)	12
	5	Psychoanaleptics (N06)	12
UK	1	Vaccines (J07)	51
	2	Antibacterials for systemic use (J01)	45
	3	Antithrombotic agents (B01)	26
	4	Other nervous system drugs (N07)	11
	5	Psychoanaleptics (N06)	11

[a]The top 5 most frequently reported therapeutic groups according to the ATC classification system (ATC second level) causing ADRs were ranked on a 5-point scale for every year by giving 5 points to the most frequently reported therapeutic group and 1 point to the least frequently reported therapeutic group. If a certain therapeutic group did not appear in the top 5 in a particular year, no points were given. The points over the whole period were added up to obtain a total score based on which the top 5 most frequently reported therapeutic groups were identified for each country

[b]For Lithuania, the top 5 ATC rank is shown for the period of 2015–2022

EU countries that implemented consumer ADR reporting systems after the 2012 EU pharmacovigilance legislation with those that had consumer reporting systems before 2012, we could not observe any obvious differences in tendencies between these two groups of countries. The ratios of HCP-to-consumer ADR reporting were significantly decreasing (indicating the increased rates of consumer reporting) in all the countries except for Canada, where an opposite significant trend toward an increasing HCP reporting rate was observed for 2012–2020. From the group of countries that implemented consumer ADR reporting systems after the 2012 EU legislation, three countries, namely Belgium, Finland, and Lithuania, had the greatest significant negative AAPC. The analysis of the ratios of serious-to-nonserious

Table 5 The top 10 most frequently reported therapeutic groups (ATC second level) causing adverse drug reactions by the total score across all countries (excluding Belgium)

ATC therapeutic subgroup	Total score[a]	Top rank
Vaccines (J07)	276	1
Immunosuppressants (L04)	148	2
Antineoplastic agents (L01)	136	3
Antibacterials for systemic use (J01)	113	4
Antithrombotic agents (B01)	94	5
Psycholeptics (N05)	58	6
Psychoanaleptics (N06)	56	7
Other gynecologicals (G02)	50	8
Analgesics (N02)	24	9
Antivirals for systemic use (J05)	18	10

[a]First, the top 5 most frequently reported therapeutic groups according to the ATC classification system (ATC second level) causing ADRs were determined as described in the footnotes of Table 4. Later, the top 10 most frequently reported therapeutic groups by the total score across all countries were determined

ADR reporting showed that Finland, Lithuania, and Portugal (countries that implemented consumer ADR reporting systems after the 2012 EU legislation) had the greatest negative AAPC; meanwhile, Canada had the smallest negative AAPC across all countries.

ADRs are associated with higher mortality rates, greater rates of hospital admission, longer hospital stays, and increased health care expenditures. A systematic review done by Howard et al. in 2006 reported that drug-related admissions in the USA accounted for 4.2%–9.6% of all admissions; in Canada, 30.7%; in Australia, 5.7%–18.8%; and in Europe, 2.5%–12.5% [26]. Up to half of ADR-related admissions are regarded as preventable [11]. Given all these estimates, the underreporting rates of ADRs can be as high as 95% [8, 9]. Despite Sweden being one of the leading countries in the world with ADR report numbers, the study by Bäckström et al. conducted at five hospitals in 2004 showed that the overall underreporting rate of serious ADRs was 86%, with an underreporting rate in one hospital being even 100% [27]. The causes of ADR underreporting by HCPs and consumers are complex [18, 28], but most likely are associated with time restrictions for reporting, lack of knowledge of how and where to report, and difficulties in recognizing ADRs, as direct causality of an ADR appears to be difficult to determine [8]. Almost 50 years ago, British physician Inman was the first to indicate so-called seven deadly sins, namely ignorance, diffidence, indifference, ambition, complacency, guilt, and fear, as the reasons for ADR underreporting by HCPs [29]. Later, these reasons were updated and additionally included lethargy, insecurity, and unavailability of notification forms. An updated systematic review by García-Abeijon in 2023 aimed at determining the factors associated with underreporting by HCPs by employing Inman's "seven deadly sins" model [28]. This review indicated ignorance and lethargy as being the main determinants of underreporting (86% and 85%, respectively) followed by complacency (46%), diffidence (45%), and insecurity (34%). It concluded that very little had changed from 2009 despite all these factors being considered potentially modifiable with the help of educational interventions [28]. A survey carried out in Finland in 2022 reported that the main reason for non-reporting an ADR indicated by HCPs was that the ADR was already known, followed by the lack of time and knowledge of how to report [30]. Those HCPs who reported an ADR more than 5 times made up only 8%, while those who had not reported any ADRs during their careers accounted for even 42%. Seriousness and unexpectedness of an ADR were the main motivating factors to report [30]. The study by Li et al. investigating why hospital-based HCPs did not report ADRs found that knowing how to report ADRs, having been trained on ADR reporting, and encountering ADRs as part of clinical practice were significant predictors of reporting ADRs [31]. According to a recent study, there is a necessity to implement strategies to recognize, report, and monitor ADRs in hospital settings [32]. Nonspecific manifestations of ADRs often lead to difficulties for clinicians in recognizing ADRs and distinguishing them from underlying conditions [33]. The study by Gautron et al. concluded that providing HCPs with clear guidance on how to identify reportable suspected serious ADRs and to assess the likelihood of causality could improve medication safety [34]. Moreover, in some countries, patient reporting systems to encourage patients' awareness to report an ADR have been promoted via HCPs, and activities to educate the public on the importance of reporting have been implemented [35].

Contribution of all HCPs, including physicians, dentists, nurses, and pharmacists, is essential to improve drug safety. For many years, physicians have been considered the key source of ADR reporting as they serve as frontline health care providers acting directly at the patient's bedside [36]. However, the role of other HCPs cannot be underestimated. Community and hospital pharmacists are highly perceived for their role in reporting ADRs in their daily practice as it is their core duties [37, 38]. Moreover, nurses are in a unique position to monitor the patient's responses to administered drugs and, consequently, to report potential ADRs if necessary [39, 40]. Unfortunately, we could not perform an analysis showing the contribution of particular HCP groups to ADR reporting as not all countries we included in our study sent the separate numbers of ADRs for every HCP group. However, using the available data, we see that pharmacists' input in ADR reporting differs across the countries. In Portugal, the percentage of ADR reports by pharmacists accounted for 40% to 50% during the 11-year period, while in Canada, the Netherlands, and Sweden, this percentage

ranged between 10 and 15% of all ADR cases reported by HCPs. Only 1% to 2% of all ADRs were reported by pharmacists in Lithuania (data not shown). Regarding ADR reporting by nurses, we found that in Portugal, the percentage of ADR reports by nurses made up 10% to 27% of all ADR reports across the different years. In Sweden, this percentage was similar, varying from 9 to 17% (with one exception being 42% in 2021 year) despite in March of 2007, Sweden issued a legislative amendment that compelled nurses to report all ADRs to the national pharmacovigilance system [40].

Under-reporting rates of ADRs could be reduced by direct patient reporting [41], and potential benefits of patient reporting have been documented in previous research. Blenkinsopp et al. summarized that patients might be more likely to identify a symptom as a suspected ADR than HCPs, might report different ADRs from those reported by HCPs, and might indicate new ADRs that had not been known [42]. Later, it was confirmed by Health Action International Europe that reports by patients were more direct as they came from persons who experienced the effects, provided more details, and were more explicit than those by HCPs [43]. Therefore, it is important to identify the factors that have an impact on voluntary patient reporting of ADRs to implement strategies for improving it [44]. Poor awareness, confusion about who should report the ADR, difficulties with reporting procedures, and lack of feedback on submitted reports have been identified as the main barriers to patient reporting of ADRs [44]. Other factors might play a role in consumers' under-reporting of ADRs as well. The ADR online registration form differs across countries; different data are collected [35, 45, 46], and the number of clicks needed to reach an online report form varies from one to five [35]. It seems that countries with the most easily accessible ADR reporting forms online have the highest numbers of ADRs.

The COVID-19 pandemic caused by SARS-CoV-2 represented an enormous challenge for health care systems. This unprecedented time of the pandemic prompted the rapid and successful development, authorization, and production of multiple vaccines within a year that resulted in massive vaccination campaigns [47, 48]. More than 13 billion vaccine doses administered during the first 2 years of vaccination [49] affected the number of ADRs reported to pharmacovigilance systems across countries. As of June 2022, the reports linked to COVID-19 vaccines accounted for 14% (around 2 million reports) of all ADR reports submitted to EudraVigilance [50], reflecting the extent of the vaccination campaigns. Our analysis confirmed the upward trends in overall ADR reporting in 2021 and 2022, especially in 2021 where 1- to 39-fold greater incidences of ADR reporting per 100,000 population across the selected countries were documented. It is worth noting that Canada was the country with the smallest change in the overall incidence rate and lowest AAPC of 10.3 (95% CI, 7.4 to 13.3). Moreover, for Canada, a different trend as compared to other countries was observed in ADR reporting by HCPs and consumers: despite we were not able to get these data for Canada for the 2021 and 2022 years, the trend in the ratio of HCP-to-consumer ADR reporting for the period 2012–2020 was opposite (AAPC of 3.9; 95% CI, 0.5 to 7.4) as compared to other countries included in our study. It might be due to public awareness as Canada was the first country that started collecting consumers' reports early on, likely around 1965, when the Canadian pharmacovigilance program was launched [51]. Among the countries included in our study, three EU countries had implemented patient reporting systems before 2012: Sweden since 1978 via KILEN, the Netherlands since 2003, and the UK since 2005 [42]. However, our study could not identify different trends in the ratio of HCP-to-consumer ADR reporting in these countries when compared with those EU countries that had no patient reporting systems implemented before 2012. Regarding serious-to-nonserious ADR reporting, Canada also stood out from other countries with significant changes: among the countries with significantly decreasing ratios of serious-to-nonserious ADR reporting, namely Finland, Lithuania, the Netherlands, and Portugal, the smallest negative AAPC being −6.8 was obtained for Canada.

During the study period, other pharmacovigilance-related initiatives that might have influenced HCP and consumer ADR reporting were launched. In Canada, the *Protecting Canadians from Unsafe Drugs Act* (Vanessa's Law), enacted in 2014, introduced some amendments to Canada's Food and Drugs Act. It included the requirements of mandatory reporting of serious ADRs and medical device events by health care institutions that came into effect in December 2019 [52]. However, this law mandates hospitals rather than HCPs to report serious ADRs, and from the very beginning, there were concerns that due to the subjectivity of HCPs to identify serious ADRs, health care institutions may face difficulties complying with this law [34]. Studies evaluating the impact of this law on the reporting of serious ADRs are scarce. The study by Djiokeng et al. aimed to determine if the enactment of Vanessa's Law led to an increased reporting of serious ADRs that occurred after antiplatelet use in a tertiary academic hospital in Quebec. It appeared to have little effect on serious ADR reporting in this study [53]. In another study by Lavallée et al., a total of 500 electronic medical records of the same health care institution in Quebec from the period of January 1, 2018, to December 31, 2021, were reviewed [54]. The study found that no serious ADR had been reported to Health Canada even after the implementation of Vanessa's Law. With the data of our study and their analysis, we cannot confirm or deny the impact of

Vanessa's Law on ADR reporting as we did not perform any cross-analysis by ADR seriousness and type of a reporter.

It is worth mentioning that the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action was initiated by a team of European regulators, which aimed at strengthening the pharmacovigilance network in Europe and improving operating pharmacovigilance capabilities and collaborative working [55]. This Joint Action in collaboration with national competent authorities and other organizations carried out additional activities such as social media awareness campaigns [55]. It has been reported that with the help of the 2017 campaign, a total of 2.3 million people were reached on social media and this led to an 11% increase in ADR reporting [56]. Despite our study showing upward trends in ADR reporting and downward trends in the ratios of HCP-to-consumer ADR reporting in EU countries, it was impossible, again, to determine the individual impact of each initiative on ADR reporting rates.

Despite the vaccination due to the COVID-19 pandemic in all countries in 2021 and its related ADR reporting, analysis of the main groups of active substances according to the ATC classification system revealed that the same drug classes remained (just they exchanged the places with each other) during the study period, and vaccine-related ADRs were among the top 5 groups of active substances causing ADRs even from 2012 (just other vaccines) in all the countries except Canada. The study conducted in Germany evaluated all suspected ADR reports from the ADR database of the German Federal Institute for Drugs and Medical Devices containing reports starting from 1978 and found that the most commonly reported top 5 therapeutic groups were antithrombotic agents (B01), antibacterials for systemic use (J01), psycholeptics (N05), psychoanaleptics (N06), and antineoplastic agents (L01) [57]. These therapeutic groups were found to be in the top 10 list of the most frequently reported drugs in our study as well. In the Finnish register-based study on emergency room admissions carried out in the tertiary hospital, the ATC therapeutic subgroups most often involved with ADRs were antithrombotic agents (B01) and antineoplastic agents (L01), followed by analgesics (N02), immunosuppressants (L04), and sex hormones and modulators of the genital system (G03) [58]. Two therapeutic groups, namely B01 and L04, can be seen in the top 10 most frequently reported drugs across all countries in our study. The 2-year data of more than 16,000 individual case safety reports from Israel showed that immunosuppressant drugs (L04 A), antineoplastic agents (L01X), and parathyroid hormones and analogues (H05 A) accounted for around 40% of all ADR reports followed by antithrombotic agents (B01 A) and blood glucose lowering drugs excluding insulin (A10B) (around 5% each) [59]. The therapeutic groups such as L04, L01, and B01 were among the top 5 most frequently reported drugs across all countries in our study.

Some limitations of this study have to be acknowledged. First, in the analysis, we included the data of only eight countries that responded. Moreover, the national authorities of some countries could not provide the complete data we asked for. Second, there is a lack of the unified data collection system among the non-EU and EU countries, and this made the analysis complicated. Future analysis should be done involving more countries to gain a better understanding of changes in ADR reporting over time. To prevent future ADRs and consequently to reduce the burden on health care, larger scale studies on the reporting patterns of ADRs by consumers and HCPs are warranted.

Conclusions

Our study shows the significant upward trends in overall ADR reporting not only in the countries that implemented patient ADR reporting systems after the 2012 EU pharmacovigilance legislation but also in the countries that had patient reporting incorporated into the pharmacovigilance systems before 2012. Moreover, significant downward trends in the ratios of HCP-to-consumer ADR reporting were documented for all EU countries, confirming increasing consumer' involvement in ADR reporting. Further, larger scale studies with the involvement of more countries are needed to better understand the trends in ADR reporting, and multifaceted interventions are warranted to be installed to enhance ADR reporting.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-025-03862-2.

Acknowledgements We would like to thank the national competent authorities of all countries that responded and kindly provided the data. Especially we are grateful to Eglė Burbienė, Head of the Pharmacovigilance and Poison Information Unit, State Medicines Control Agency, Lithuania, and Dennis Smits, Data Scientist of the Medicines Evaluation Board, the Netherlands.

Author contribution E.S. and E.K. contributed to the study conception and design. Material preparation, data collection and analysis were performed by G.M. The first draft of the manuscript was written by G.M. and all authors commented on subsequent versions of the manuscript. All authors read and approved the final version of the manuscript.

Data availability No datasets were generated or analysed during the current study.

Code availability The code of this study is available from the corresponding author upon reasonable request.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Le Louët H, Pitts PJ (2023) Twenty-first century global ADR management: a need for clarification, redesign, and coordinated action. Ther Innov Regul Sci 57:100–103. https://doi.org/10.1007/s43441-022-00443-8
2. Durand M, Castelli C, Roux-Marson C, Kinowski J, Leguelinel-Blache G (2024) Evaluating the costs of adverse drug events in hospitalized patients: a systematic review. Health Econ Rev 14:11-y. https://doi.org/10.1186/s13561-024-00481-y
3. International drug monitoring: the role of national centres. Available online: https://iris.who.int/bitstream/handle/10665/40968/WH?sequence=1. (Accessed 9 June 2024)
4. Proposal for a regulation amending, as regards pharmacovigilance of medicinal products for human use. Regulation (EC) No 726/2004. Impact assessment. Available online: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52008SC2671
5. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA, J Am Med Assoc 279:1200–1205. https://doi.org/10.1001/jama.279.15.1200.Availableonline:doi:10.1001/jama.279.15.1200
6. Patel TK, Patel PB (2018) Mortality among patients due to adverse drug reactions that lead to hospitalization: a meta-analysis. Eur J Clin Pharmacol 74:819–832. https://doi.org/10.1007/s00228-018-2441-5
7. Bouvy JC, De Bruin ML, Koopmanschap MA (2015) Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf 38:437–453. https://doi.org/10.1007/s40264-015-0281-0
8. Carleton BC, Smith MA (2006) Drug safety: side effects and mistakes or adverse reactions and deadly errors? BCMJ 48:329–333
9. Adverse Drug Reactions. Available online: https://cpnds.ubc.ca/about/ (Accessed on 5 November 2023).
10. Sultana J, Cutroneo P, Trifirò G (2013) Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother 4:S73–S77. https://doi.org/10.4103/0976-500X.120957. Available online: https://www.ncbi.nlm.nih.gov/pubmed/24347988
11. Ehsani JP, Jackson T, Duckett SJ (2006) The incidence and cost of adverse events in Victorian hospitals 2003–04. Med J Aust 184:551–555. https://doi.org/10.5694/j.1326-5377.2006.tb00378.x. Available online: https://search.informit.org/documentSummary;res=IELAPA;dn=200606144
12. Osanlou R, Walker L, Hughes DA, Burnside G, Pirmohamed M (2022) Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. BMJ Open 12. https://doi.org/10.1136/bmjopen-2021-055551
13. Safety monitoring of medical products: reporting system for the general public. Available online: https://apps.who.int/iris/bitstream/handle/10665/336225/9789241503198-eng.pdf?sequence=1&isAllowed=y. (Accessed 13 June 2024)
14. Herdeiro MT, Figueiras A, Polónia J, Gestal-Otero JJ (2005) Physicians' attitudes and adverse drug reaction reporting : a case-control study in Portugal. Drug Saf 28:825–833. https://doi.org/10.2165/00002018-200528090-00007
15. Lopez-Gonzalez E, Herdeiro MT, Figueiras A (2009) Determinants of under-reporting of adverse drug reactions. Drug safety : an international journal of medical toxicology and drug experience 32:19–31. https://doi.org/10.2165/00002018-200932010-00002
16. Inácio P, Cavaco A, Airaksinen M (2017) The value of patient reporting to the pharmacovigilance system: a systematic review. Br J Clin Pharmacol 83:227–246. https://doi.org/10.1111/bcp.13098
17. Ancel.la Santos. Direct patient reporting in the European Union. A snapshot of reporting systems in seven member states. **2015** Available online: https://haiweb.org/wp-content/uploads/2015/09/Direct-Patient-Reporting-in-the-EU.pdf
18. Costa C, Abeijon P, Rodrigues DA, Figueiras A, Herdeiro MT, Torre C (2023) Factors associated with underreporting of adverse drug reactions by patients: a systematic review. Int J Clin Pharm 45:1349–1358. https://doi.org/10.1007/s11096-023-01592-y
19. Arlett P, Portier G, de Lisa R, Blake K, Wathion N, Dogne J, Spooner A, Raine J, Rasi G (2014) Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. Nat Rev Drug Discov 13:395–397. https://doi.org/10.1038/nrd3713-c1
20. Banovac M, Candore G, Slattery J, Houÿez F, Haerry D, Genov G, Arlett P (2017) Patient reporting in the EU: analysis of EudraVigilance data. Drug Saf 40:629–645. https://doi.org/10.1007/s40264-017-0534-1
21. Margraff F, Bertram D (2014) Adverse drug reaction reporting by patients: an overview of fifty countries. Drug Saf 37:409–419. https://doi.org/10.1007/s40264-014-0162-y
22. van Hunsel F, Härmark L, Pal S, Olsson S, van Grootheest K (2012) Experiences with adverse drug reaction reporting by patients. Drug Saf 35:45–60. https://doi.org/10.2165/11594320-000000000-00000. Available online: https://link.springer.com/article/https://doi.org/10.2165/11594320-000000000-00000
23. Reported side effects following COVID-19 vaccination in Canada. Available online: https://health-infobase.canada.ca/covid-19/vaccine-safety/ (Accessed on Accessed on 13 February 2025).
24. Anatomical Therapeutic Chemical (ATC) Classification. Available online: https://www.who.int/tools/atc-ddd-toolkit/atc-classification#:~:text=In%20the%20Anatomical%20Therapeutic%20Chemical,groups%20at%20five%20different%20levels (Accessed on 24 March 2025).
25. European Medicines Agency. Serious adverse reaction. Available online: https://www.ema.europa.eu/en/glossary/serious-adverse-reaction. (Accessed 6 July 2024)
26. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, Pirmohamed M (2007) Which drugs cause preventable

admissions to hospital? A systematic review. Br J Clin Pharmacol 63:136–147. https://doi.org/10.1111/j.1365-2125.2006.02698.x
27. Bäckström M, Mjörndal T, Dahlqvist R (2004) Under-reporting of serious adverse drug reactions in Sweden. Pharmacoepidemiol Drug Saf 13:483–487. https://doi.org/10.1002/pds.962
28. García-Abeijon P, Costa C, Taracido M, Herdeiro MT, Torre C, Figueiras A (2023) Factors associated with underreporting of adverse drug reactions by health care professionals: a systematic review update. Drug Saf 46:625–636. https://doi.org/10.1007/s40264-023-01302-7
29. Inman W, Gent M, Shigmatsu I (1976) Epidemiological issues in reported drug-induced illnesses. McMaster University Library Press Honolulu 17–24
30. Sandberg A, Salminen V, Heinonen S, Sivén M (2022) Under-reporting of adverse drug reactions in Finland and healthcare professionals' perspectives on how to improve reporting. Healthcare (Basel) 10:1015. https://doi.org/10.3390/healthcare10061015. Available online: https://search.proquest.com/docview/2679715750
31. Li R, Curtis K, Van C, Zaidi TRS, Yeo CY, Arun Kali C, Zaheen M, Therese Moujalli G, Castelino R (2022) Why hospital-based healthcare professionals do not report adverse drug reactions: a mixed methods study using the Theoretical Domains Framework. Eur J Clin Pharmacol 78:1165–1175. https://doi.org/10.1007/s00228-022-03326-x
32. Aung AK, Walker S, Khu YL, Tang MJ, Lee JI, Graudins LV (2022) Adverse drug reaction management in hospital settings: review on practice variations, quality indicators and education focus. Eur J Clin Pharmacol 78:781–791. https://doi.org/10.1007/s00228-022-03287-1. Available online: https://link.springer.com/article/https://doi.org/10.1007/s00228-022-03287-1
33. Hire Rohan C, Kinage Parag J, Gaikwad Nilesh N (2013) Causality assessment in pharmacovigilance: a step towards quality care. Sch J Appl Med Sci 1:386–392, https://doi.org/10.36347/sjams.2013.v01i05.008. Available online: https://saspublishers.com/media/articles/SJAMS15386-392_w8SI0KZ.pdf
34. Gautron S, Wentzell J, Kanji S, Nguyen T, Kobewka DM, MacDonald E (2018) Characterization of serious adverse drug reactions in hospital to determine potential implications of mandatory reporting. Canadian journal of hospital pharmacy 71:316–323. https://doi.org/10.4212/cjhp.v71i5.2842. Available online: https://www.ncbi.nlm.nih.gov/pubmed/30401998
35. Worakunphanich W, Youngkong S, Suwankesawong W, Anderson C, Thavorncharoensap M (2022) Comparison of patient adverse drug reaction reporting systems in nine selected countries. Int J Environ Res Public Health 19:4447. https://doi.org/10.3390/ijerph19084447. Available online: https://www.ncbi.nlm.nih.gov/pubmed/35457318
36. Hussain R, Hassali MA, Ur Rehman A, Muneswarao J, Hashmi F (2020) Physicians' understanding and practices of pharmacovigilance: qualitative experience from a lower middle-income country. Int J Environ Res Public Health 17:2209. https://doi.org/10.3390/ijerph17072209
37. Elkalmi RM, Hassali MA, Ibrahim MIM, Jamshed SQ, Al-lela O (2014) Community pharmacists' attitudes, perceptions, and barriers toward adverse drug reaction reporting in Malaysia: a quantitative insight. Journal of Patient Safety 10. Available online: https://journals.lww.com/journalpatientsafety/fulltext/2014/06000/community_pharmacists__attitudes,_perceptions,_and.1.aspx
38. Hadi MA, Neoh CF, Zin RM, Elrggal ME, Cheema E (2017) Pharmacovigilance: pharmacists' perspective on spontaneous adverse drug reaction reporting. Integr Pharm Res Pract 6:91–98. https://doi.org/10.2147/IPRP.S105881
39. De Angelis A, Giusti A, Colaceci S, Vellone E, Alvaro R (2015) Nurses' reporting of suspect adverse drug reactions: a mixed-methods study. Ann Ist Super Sanita 51:277–283. https://doi.org/10.4415/ANN_15_04_06
40. Karlsson SA, Jacobsson I, Boman MD, Hakkarainen KM, Lövborg H, Hägg S, Jönsson AK (2015) The impact of a changed legislation on reporting of adverse drug reactions in Sweden, with focus on nurses' reporting. Eur J Clin Pharmacol 71:631–636. https://doi.org/10.1007/s00228-015-1839-6
41. Hazell L, Shakir SAW (2006) Under-reporting of adverse drug reactions. Drug Saf 29:385–396. https://doi.org/10.2165/00002018-200629050-00003.Availableonline:doi:10.2165/00002018-200629050-00003
42. Blenkinsopp A, Wilkie P, Wang M, Routledge PA (2007) Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol 63:148–156. https://doi.org/10.1111/j.1365-2125.2006.02746.x
43. Herxheimer Andrew; Crombag Rose; Leonardo Alves Teresa Direct patient reporting of adverse drug reactions. **2010** Available online: https://consumers.cochrane.org/sites/consumers.cochrane.org/files/uploads/10%20May%202010%20Report%20Direct%20Patient%20Reporting%20of%20ADRs.pdf.
44. Al Dweik R, Stacey D, Kohen D, Yaya S (2017) Factors affecting patient reporting of adverse drug reactions: a systematic review. Br J Clin Pharmacol 83:875–883. https://doi.org/10.1111/bcp.13159
45. Singh A, Bhatt P (2012) Comparative evaluation of adverse drug reaction reporting forms for introduction of a spontaneous generic ADR form. J Pharmacol Pharmacother 3:228–232. https://doi.org/10.4103/0976-500X.99417
46. Maharshi V, Nagar P (2017) Comparison of online reporting systems and their compatibility check with respective adverse drug reaction reporting forms. Indian J Pharmacol 49:374–382. https://doi.org/10.4103/ijp.IJP_733_16
47. Pardo-Cabello AJ, Manzano-Gamero V, Luna JDR (2023) Differences in reporting of adverse drug reactions due to COVID-19 vaccines depending on the reporter. Eur J Intern Med 113:104–106. https://doi.org/10.1016/j.ejim.2023.03.020
48. Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C, Giattino C, Rodés-Guirao L (2021) A global database of COVID-19 vaccinations. Nat Hum Behav 5:947–953. https://doi.org/10.1038/s41562-021-01122-8.Availableonline:doi:10.1038/s41562-021-01122-8
49. Total COVID-19 vaccine doses administered. Available online: https://ourworldindata.org/grapher/cumulative-covid-vaccinations?time=earliest..2021-12-01&facet=none&country=~OWID_WRL (Accessed on 15–02 2025).
50. Durand J, Dogné J, Cohet C, Browne K, Gordillo-Marañón M, Piccolo L, Zaccaria C, Genov G (2023) Safety monitoring of COVID-19 vaccines: perspective from the European Medicines Agency. Clin Pharmacol Ther 113:1223–1234. https://doi.org/10.1002/cpt.2828.Availableonline:doi:10.1002/cpt.2828
51. Napke Ed. A lifetime in safety. Selected articles by Ed Napke. **2010**, 107. https://view.publitas.com/uppsala-monitoring-centre/a-lifetime-in-safety/page/1. (Accessed 13 July 2024)
52. Module 1: Overview of Vanessa's Law and reporting requirements. Available online: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-react

ion-reporting/mandatory-hospital-reporting/education/module-1.html (Accessed on 13 February 2025).
53. Guefack Djiokeng LB, Todkar S, Corbin S, Lavallée M, Pradhan P, Thibault M, Piché M, Méthot J, Bérard A, Gonella JM, Escobar Gimenes FR, Darveau R, Cloutier I, Leclerc J (2024) Impact of Vanessa's Law on the reporting of serious adverse events: a retrospective study among antiplatelet users in a tertiary-care cardiology centre. CJC Open 6:1527–1533. https://doi.org/10.1016/j.cjco.2024.09.003
54. Lavallée M, Corbin S, Pradhan P, Guefack LB, Thibault M, Méthot J, Bérard A, Piché M, Gimenes FRE, Darveau R, Cloutier I, Leclerc J (2024) Underreporting of adverse events to health authorities by healthcare professionals: a red flag-raising descriptive study. Int J Qual Health Care 36:mzae109. https://doi.org/10.1093/intqhc/mzae109. https://doi.org/10.1093/intqhc/mzae109
55. Radecka A, Loughlin L, Foy M, de Ferraz Guimaraes MV, Sarinic VM, Di Giusti MD, Lesicar M, Straus S, Montero D, Pallos J, Ivanovic J, Raine J (2018) Enhancing pharmacovigilance capabilities in the EU regulatory network: the SCOPE joint action. Drug Saf 41:1285–1302. https://doi.org/10.1007/s40264-018-0708-5
56. Campaign raises awareness of medicines safety in children and pregnancy. Available online: https://uppsalareports.org/articles/campaign-raises-awareness-of-medicines-safety-in-children-and-pregnancy/ (Accessed on 15 February 2025).
57. Dubrall D, Schmid M, Alešik E, Paeschke N, Stingl J, Sachs B (2018) Frequent adverse drug reactions, and medication groups under suspicion. Dtsch Arztebl Int 115:393–400. https://doi.org/10.3238/arztebl.2018.0393
58. Kauppila M, Backman JT, Niemi M, Lapatto-Reiniluoto O (2021) Incidence, preventability, and causality of adverse drug reactions at a university hospital emergency department. Eur J Clin Pharmacol 77:643–650. https://doi.org/10.1007/s00228-020-03043-3
59. Schwartzberg E, Berkovitch M, Dil Nahlieli D, Nathan J, Gorelik E (2017) Pharmacovigilance in Israel - tools, processes, and actions. Isr J Health Policy Res 6:29–33. https://doi.org/10.1186/s13584-017-0154-3

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