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ORIGINAL RESEARCH ARTICLE

Patient Reporting in the EU: Analysis of EudraVigilance Data

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Abstract

Introduction New pharmacovigilance legislation was adopted in the EU in 2010 and became operational in July 2012. The legislation placed an obligation on all national competent authorities (NCAs) and marketing authorisation holders (MAHs) to record and report cases of suspected adverse drug reactions (ADRs) received from patients.

Objectives This descriptive study aims to provide insight into patient reporting for the totality of the EU by querying the EudraVigilance (EV) database for the period of 3 years before the new pharmacovigilance legislation became operational and the 3 years after as well as comparing patient reports with those from healthcare professionals (HCPs) where feasible.

Methods We queried the EV database for the following characteristics of patient and HCP reports: demographics (patient sex and age), seriousness, reported ADR terms, reported indications, number of ADRs per report, time to report an ADR, and most reported substances. Wherever feasible, direct comparisons between patient reports and HCP reports were performed using relative risks.

Results The EV database contained a total of 53,130 patient reports in the 3 years preceding the legislation operation period and 113,371 in the 3 years after. Member states contributing the most patient reports to the EV database were the Netherlands, the UK, Germany, France and Italy. The results for indications and substances show that patients were more likely than HCPs to report for genitourinary, hormonal and reproductive indications. Patients reported more in general disorders and administration site conditions Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), whereas HCPs reported more Preferred Terms (PTs) belonging in the Investigations SOC. However, 13 of the 20 reactions most frequently reported by patients were also among the top 20 reactions reported by HCPs.

Conclusion Patient reporting complemented reporting by HCPs. Patients were motivated to report ADRs, especially those that affected their quality of life. Sharing these results with NCAs and patient associations can inform training and awareness on patient reporting.

Key Points

This is the largest study to date, by sample size, on patient adverse drug reaction (ADR) reporting that represents the whole EU.

The growing numbers of patient reports indicate patients' high motivation to report ADRs in the EU and suggests the new EU pharmacovigilance legislation has made a positive impact by empowering patients.

While the most frequent reaction terms from patients and healthcare professionals overlap, patient reports more often cover reactions affecting quality of life. The results suggest that the two reporting sources are complementary in drug safety monitoring.

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1 Introduction

While medicines save lives and reduce suffering, adverse drug reactions (ADRs) are a common public health concern. Previous research has consistently shown that 5–7% of hospital admissions are due to ADRs [1–3]. In addition to having a significant impact on a patient's life, ADRs are also detrimental to healthcare systems. A 2004 study estimated the annual cost of UK hospitalizations due to mostly avoidable ADRs was over €700 million [1]. In 2008, the European Commission estimated the annual EU-wide societal cost of ADRs was €79 billion and 197,000 deaths [4].

Spontaneous reporting of ADRs is a cornerstone of the post-marketing safety surveillance of medicinal products. This especially concerns serious and rare ADRs that could not have been detected during the pre-authorisation phase of drug development because of the low or short duration of exposure of patients to drugs in clinical trials. Acquiring information based on spontaneous reporting of ADRs facilitates prevention of ADRs as well as the management of risks associated with the use of medicinal products. Although some countries established systems for ADR reporting by patients decades ago (e.g. Australia started accepting patient reports in 1964 [5]), until the 2000s the reporting of ADRs was mostly restricted to healthcare professionals (HCPs) [6] in most countries. In 2003, Denmark and the Netherlands, followed by Italy (2004), the UK (2005), Sweden (2008) [7] and Croatia (2009) [8] allowed patients to report directly to their regulatory agency. Earlier studies of the impact of patient reporting on signal generation found the available data insufficient to draw conclusions [9, 10] or gave only a hint of potential usefulness of patient reporting with a call for further research; however, over time, the body of evidence accumulated to the point that patients' contributions to spontaneous ADR reporting was positively valued and calls began to be made for its widespread introduction [11–15]. A recent systematic review of the literature on patient reporting concluded that "patient reporting adds new information and perspective about ADRs in a way otherwise unavailable" [16].

In 2010, new pharmacovigilance legislation was adopted in the EU. One of the key provisions of this legislation was to place an obligation on all national competent authorities (NCAs) for medicines in the European Economic Area (EEA), and all marketing authorisation holders (MAHs), to record and report cases of suspected adverse reactions reported by patients [17]. Furthermore, feedback from patient groups suggested that patients wanted to be empowered by having the ability to directly report suspected adverse reactions [18]. Patient representatives were involved in implementation planning of the new pharmacovigilance legislation as well as in creating promotional materials for patients on how to report an ADR and the concept of the 'black triangle' (drugs under additional monitoring) [19].

2 Aims

Numerous analyses have covered various aspects of patient reporting [5, 10–13, 15, 18]. Most of these studies relied on data from a restricted number of countries since patient reporting was not mandatory in the EU when these studies were performed, or the research involved surveying NCAs. The current study aims to provide insight into patient reporting for the totality of the EU by querying the EudraVigilance (EV) database. As the new pharmacovigilance legislation officially became operational in July 2012 [20], we describe patient reporting for the 3 years before and 3 years after this important milestone.

This study describes the characteristics of patient reports and identifies the changes to patient reporting patterns resulting from the implementation of the new EU pharmacovigilance legislation and compares patient reports with HCP reports, in terms of the following:

- number of reports and their proportion in EV over time, and the contribution of reports from individual member states
- patient characteristics (sex and age groups)
- seriousness profile and presence of either a designated medical event term or an important medical event term or both
- most frequently reported reactions and System Organ Classes (SOCs)
- most frequently reported medicines and indications
- time elapsed between the onset of the adverse reaction and reporting of the reaction.

Analysis of the patient reports received in the EV, and identifying potential gaps in reporting may (1) inform the provision of information and training to patients, (2) support better collaboration with patient associations, (3) support better communication campaigns on the awareness of reporting suspected ADRs and (4) inform improved approaches to the analysis of reports for future safety signal detection and evaluation.

3 Methods

EV is the European database and data processing network for both clinical trial suspected unexpected serious adverse reactions and reports of suspected ADRs from marketed use. During the period of this study, EU legislation required NCAs and MAHs to report all serious suspected ADRs from marketed use from within the EEA. While EV

contains both study and spontaneous reports from marketed use, we only queried EV for all *spontaneous reports that originated in the EEA* regardless of the sender (i.e. regulatory authority or pharmaceutical company) [21]. We used the reporter qualification field (E2B field A.2.1.4)[1] to identify the primary source of the report, which led us to create the following groups:

- 'Only Patient': reports where "consumer or other non-health professional" was the only primary source qualification.
- 'Only HCP': reports where an HCP (i.e. physician, pharmacist or other) was the only primary source qualification.
- 'All Patient': reports where "consumer or other non-health professional" was one of the primary source(s) qualification. This included the HCP as a co-reporter, but excluded legal reports.[2]
- 'Legal': any report where a lawyer was a primary source qualification, independent of whether patients or HCPs were also primary sources.

Each individual case safety report (ICSR) belonging to the same case was counted separately, i.e. initial reports and follow-up were counted as two reports because one of the primary measures of this study was the level of reporting, and each ICSR is a unit of reporting.

If patient age was not reported, it was calculated based on the difference between date of birth and reaction-onset date.

The relative risk (RR) statistic was used to show whether patients were more or less likely than HCPs to report a certain reaction or substance. RR was calculated as the ratio of the probability of an event being reported in the patient group to the probability of the event being reported in the HCP group. RR values >1 favoured patients as reporters, whereas values of RR <1 favoured HCPs.

We queried EV for the presence of either 'important medical event' (IME) or 'designated medical event' (DME) terms or both terms in ICSRs and compared patient and HCP reports. This was done because both IMEs and DMEs can be used as an indicator of reports most relevant for detecting important safety issues. The IME list was created to facilitate both the classification of suspected adverse reactions and the pharmacovigilance data analysis activities of stakeholders in the EU. Its development is co-ordinated by The EV Expert Working Group [22]. Terms included in the IME list are selected according to the official International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) definition of seriousness and of an 'important medical event'. The IME list in version 19.0 of the Medical Dictionary for Regulatory Activities (MedDRA) contains 7941 terms. The DME list was designed to prioritise the screening of specific MedDRA Preferred Terms (PTs) for signal detection activities at the European Medicines Agency (EMA) and NCAs. The version of the DME list used for this analysis contained 98 terms considered serious and associated with the use of medicines; the vast majority were also IMEs.

For practical purposes, we use the terms "before and after the new legislation" to refer to the periods before and after the implementation of the new pharmacovigilance legislation (2 July 2012) and not the dates on which the directive and regulation were adopted. We acknowledge that different member states introduced patient reporting at different times, but we used the July 2012 date for analysis and practical purposes. Statistical analyses were performed using SAS version 9.3.

4 Results

To gain as much clarity as possible about patients' ADR reporting, the main focus of the research was reports provided solely by patients (or otherwise non-HCPs): the 'Only Patient' group.

The 'All Patient' group contains both the 'Only Patient' reports and the reports for which the patient and HCP were both listed as primary sources, making 'All Patient' a heterogeneous group of reports in terms of primary sources. Therefore, the 'All Patient' group was used only to present the totality of patient reporting in the EEA, whereas the 'Only Patient' group was used for comparisons between reporter groups.

4.1 General

Overall, the number of patient reports rose year on year. In the 3 years preceding the implementation of the new pharmacovigilance legislation, the number of ICSRs reported solely by patients (Only Patient) and submitted to EV was 53,130; in the 3 years after, it was 113,371, an increase of over 60,000 reports (113%) for the 3-yearly period (Table 1). By comparison, HCPs (Only HCP) submitted 570,566 and 705,251 reports in the pre- and post-legislation period, respectively, an increase of 134,685 reports (23.6%).[3]

[1] E2B has been developed as a guideline to standardize the data elements for transmission of individual case safety reports. It is agreed within the scope of the ICH between the three medicines regulatory regions (EU, Japan and USA).

[2] Only Patient is a subset of All Patient.

[3] Note that a backlog of reports from industry that were submitted to EV in 2009 was excluded from the counts when trends were calculated (Table 1; Fig. 1) since those reports refer to the period before 2009 and distort the results. Furthermore, a high number of reports associated with the influenza pandemic was received from the Netherlands in 2009, and these reports were also excluded for trend analysis.

Table 1 Number of individual case safety reports per year and group of analysis

Primary source	July 09–July 10	July 10–July 11	July 11–July 12	Total pre	July 12–July 13	July 13–July 14	July 14–July 15	Total post
Only Patient	14,425	17,125	21,580	53,130	32,722	35,474	45,175	113,371
Only HCP	190,132	185,529	194,905	570,566	220,623	243,235	241,393	705,251
All Patient	35,121	33,420	35,140	103,681	50,560	49,561	59,220	159,341
Legal	323	552	1919	2794	953	1448	1433	3834
Not reported[a]	11,702	563	1	12,266	3	1	0	4
Total EEA spontaneous	237,278	220,064	231,965	689,307	272,139	294,245	302,046	868,430

EEA European economic area, *HCP* healthcare professional

[a] Reports without the primary source listed

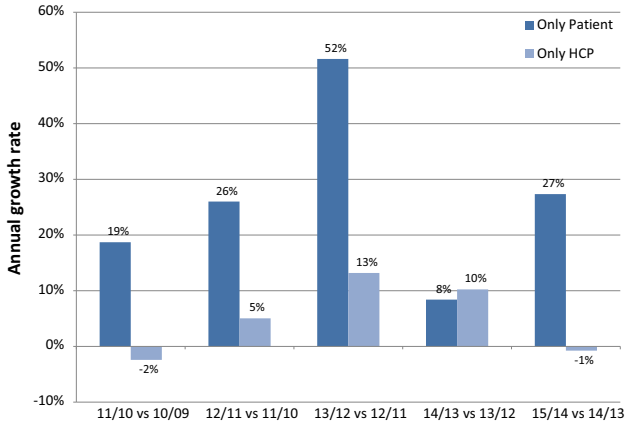


Fig. 1 Annual growth rates of spontaneous reports in EudraVigilance since 2009 for Only Patient and Only Healthcare Professional (HCP). 11/10 vs. 10/09 represents the reporting year 2 July 2010–1 July 2011 compared with 2 July 2009–1 July 2010

The greatest increase in the number of reports by Only Patient and Only HCP was observed in the first year of the implementation of the new legislation (2 July 2012–1 July 2013) as shown in Fig. 1. The Only Patient group by far exceeded the rate of growth of all spontaneous EV.

4.2 Member States

The results from the last year of study with the data lock point between 2 July 2014 and 1 July 2015 represent the most recent data for patient reporting in the EEA (Only Patient). For this period, analysis of data from all EEA countries shows 88 patient reports were received per million inhabitants of the EEA (as mentioned, the 'All Patient' category was used to represent the totality of patient reporting). The Netherlands stands out, with 706 patient reports per million inhabitants. Figure 2 shows the number of patient reports per million inhabitants per member state.

In absolute terms, member states contributing the highest number of patient reports in 2014/2015 were the Netherlands (11,938), the UK (11,370), Germany (9764), France (6082) and Italy (5127), accounting for 75% of all patient reports received in EV in the period. The same five member states contributed 77% of all HCP reports to EV.

4.3 Demographics

4.3.1 Patient Sex

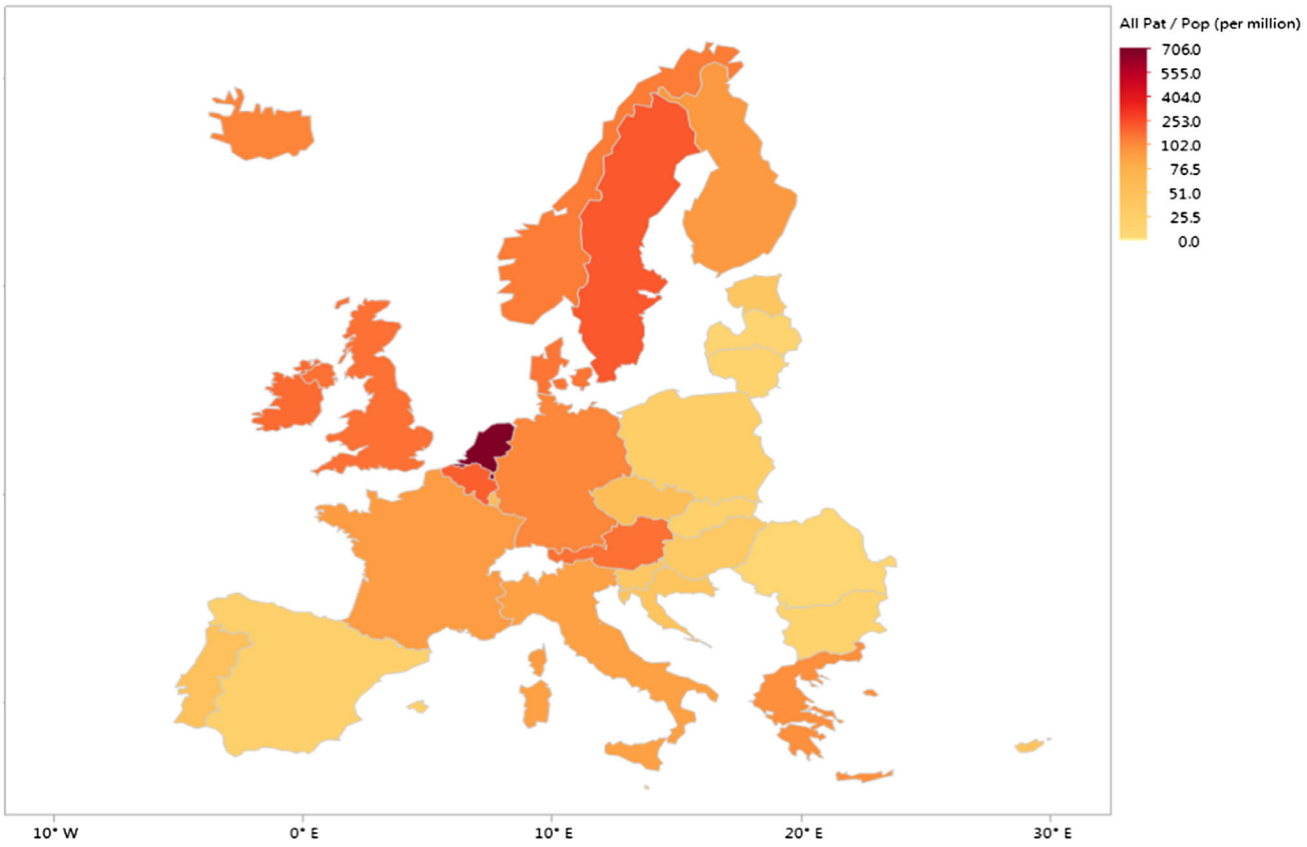
The ratio of patient reports from women versus men is, on average, 1.6 in favour of women as subjects of an ADR report (Table 2). This is in line with previous research on sex differences with ADRs [24, 25] that indicated female patients were at 1.5- to 1.7-fold greater risk of being the subject of an ADR report. No notable difference was observed according to the reporting year. HCPs reported more ADRs in male patients than did patients; however, women still make up the majority of subjects in HCP reports (ratio of 1.2–1.3; Table 2).

4.3.2 Patient Age

No trends in patient age for either patient or HCP reports were observed before or after the implementation of the new legislation. Patients reported age slightly less frequently than did HCPs (on average, more than 20 and 14% missing values, respectively). The median age for both females and males was 41 years in patient reports and was 50 and 53 years, respectively, in HCP reports (Figs. 3, 4).

4.4 Seriousness

As a rule, until July 2012, senders (NCAs and MAHs) were only obliged to send serious reports to EV. However, non-serious reports from several member states were also accepted. After the new pharmacovigilance legislation was implemented, a transitional period was put in place to enable all stakeholders to adapt to the change in EV



	EU mean	AT	BE	BG	CY	CZ	DE	DK	EE	ES	FI	FR	GB	GR	HR	HU	IE	IS	IT	LI	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
All Patient Reports per Million	116.3	172	218	19	45	58	121	162	43	24	94	93	176	102	46	36	188	125	89	0	18	59	14	40	706	145	26	52	12	234	41	21

Fig. 2 Patient reports per million inhabitants in the European economic area between July 2014 and July 2015. Patient reports are based on the EudraVigilance All Patient group. Reporting rates per million inhabitants were calculated based on the numbers of patient reports in EudraVigilance and the member states' population data provided by Eurostat [23]. For the European Economic Area map presenting the ratio of Only Patient over Only HCP reports see Fig. 1 in the Electronic Supplementary Material. *AT* Austria, *BE* Belgium, *BG* Bulgaria, *CY* Cyprus, *CZ* Czech Republic, *DE* Germany, *DK* Denmark, *EE* Estonia, *ES* Spain, *FI* Finland, *FR* France, *GB* Great Britain, *GR* Greece, *HR* Croatia, *HU* Hungary, *IE* Ireland, *IS* Iceland, *IT* Italy, *LI* Liechtenstein, *LT* Lithuania, *LU* Luxembourg, *LV* Latvia, *MT* Malta, *NL* The Netherlands, *NO* Norway, *PL* Poland, *PT* Portugal, *RO* Romania, *SE* Sweden, *SI* Slovenia, *SK* Slovakia

Table 2 Individual case safety reports (%) by patient sex stratified by the type of primary source

Primary source	Patient sex	July 09–July 10	July 10–July 11	July 11–July 12	Total pre	July 12–July 13	July 13–July 14	July 14–July 15	Total post
Only Patient	Male	37	36	34	36	36	37	35	36
	Female	61	58	61	60	61	60	62	61
	Missing	2	6	5	4	3	3	3	3
Only HCP	Male	41	41	40	41	41	42	43	42
	Female	54	52	54	53	53	54	53	53
	Missing	4	8	6	6	5	4	4	5

HCP healthcare professional

business rules. This transitional period is expected to end in late 2017 (pending the successful outcome of an audit of the new EV system) [26]. After the transitional period ends, NCAs and MAHs will also be required to send all non-serious reports to EV. As such, the results of the seriousness of patient and HCP reports should be interpreted cautiously, as they might change once the new business rules become fully operational.

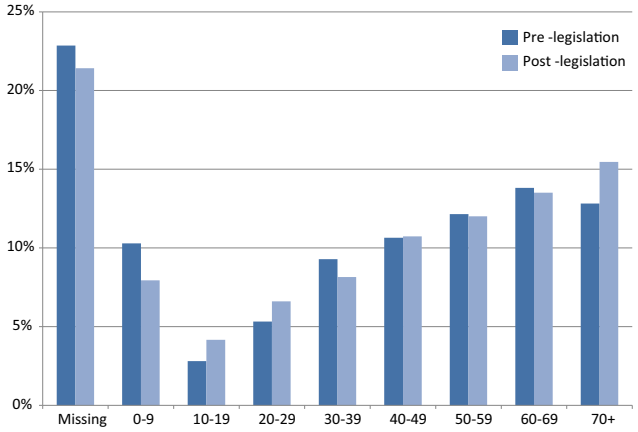


Fig. 3 Distribution of age groups by decade in Only Patient reports in EudraVigilance

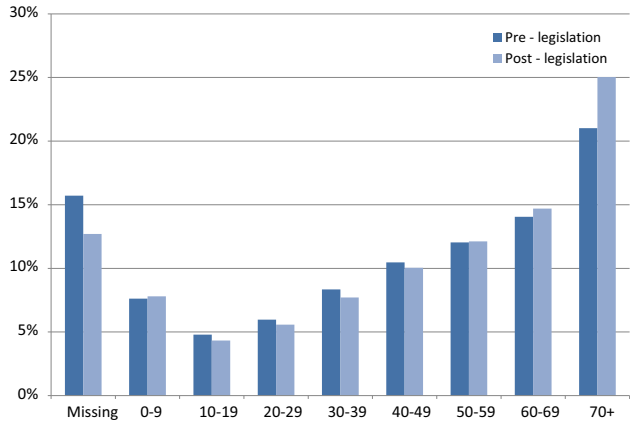


Fig. 4 Distribution of age groups by decade in only healthcare professional reports in EudraVigilance

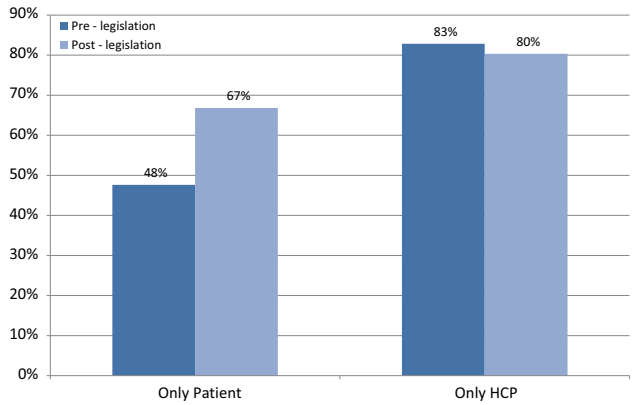


Fig. 5 The proportion of serious reports in EudraVigilance before and after the implementation of the new pharmacovigilance legislation by primary source(s). *HCP* healthcare professional

In the Only Patient category, the percentage of serious reports increased after the legislation was implemented (Fig. 5). A further analysis of this group indicated the increase was attributable to MAHs, who sent an average of 93% of serious reports in the 3 years post-legislation (the ratio of MAH: NCA serious reports in the Only Patient group in the post-legislation period was 2:1).

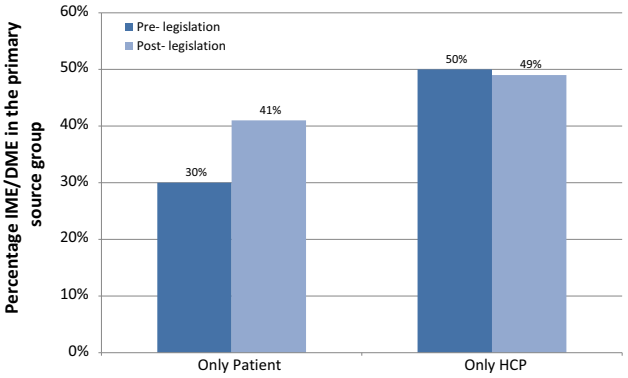


Fig. 6 Comparison of the percentage of reports containing important medical event/designated medical event (IME/DME) terms by primary source(s) before and after implementation of the new pharmacovigilance legislation. Presence of at least one IME and/or DME term on a report was used as a criterion for inclusion to IME/DME category

The percentage of fatal cases reported in 2014/15 was 3 and 6% for the Only Patient and Only HCP groups, respectively (see also Tables 5, 6 in the Electronic Supplementary Material [ESM]).

A small subset of reports co-reported by patients and HCPs contained a higher percentage of serious reports (89% pre legislation and 93% post legislation) than even the Only HCP group.

4.4.1 Important Medical Event/Designated Medical Event

In the Only Patient and Only HCP groups, 37 and 49% of reports, respectively, contained either an IME term or a DME term, or both (2009–2015 period). A notable difference was observed in patient reports (Only Patient): the proportion of reports containing an IME/DME term rose from 30% before the legislation to 41% after the legislation (Fig. 6). This increase was driven by MAHs as, on average, more than 90% of MAH reports sent to EV in the post-legislation period were serious, whereas the ratio of serious to non-serious Only Patient reports sent by NCAs was stable over time at approximately 45:55 in favour of serious reports.

4.5 Reactions

4.5.1 System Organ Classes

The top three SOCs reported by the Only Patient group in the 2009–2015 period were general disorders, nervous system disorders and gastrointestinal disorders (Fig. 7).

The order of the most frequently reported SOCs by any primary source changed slightly after the legislation, but these changes were minimal and likely to be attributed to random fluctuations in reporting (see Tables 1, 2 in the ESM).

At the SOC level, patients did not report very differently from HCPs. The top three SOCs, representing at least 30% of all reports in each primary source category, were the same for all primary sources except for the Only HCP group. For this group, after the new legislation, gastrointestinal disorders changed place with skin and subcutaneous disorders as the third most frequently reported SOC (Table 2 in the ESM). As expected, HCPs reported more PTs belonging to the Investigations SOC, whereas patients reported more for general disorders and administration site condition SOCs.

Another question of interest is which SOCs patients were more likely than HCPs to report. The likelihood of reporting by Only Patient group was calculated relative to the Only HCP group and expressed as an RR (Fig. 8).

Patients more likely to report than healthcare professionals (HCPs) Patients alone and patients and HCPs together were statistically significantly more likely than HCPs alone to report reactions belonging to the following SOCs: reproductive system and breast disorders, social circumstances, ear and labyrinth disorders, musculoskeletal and connective tissue disorders, eye disorders, psychiatric disorders, general disorders and administration site conditions, nervous system disorders, and gastrointestinal disorders.

Patients less likely to report than HCPs In contrast, patients alone were 4, 2.5 and 2 times less likely than HCPs alone to report reactions belonging to blood and lymphatic system disorders, hepatobiliary disorders, and immune system disorders, respectively (Fig. 8).

4.5.2 Preferred Terms (PTs)

The PTs most frequently reported by the Only Patient group largely reflected the results for the most frequently reported SOCs, which showed that patients most frequently reported terms belonging to general disorders and administration site conditions, nervous system disorders, and gastrointestinal disorders SOCs. Table 3 shows the 20 most reported PTs for the Only Patient group and ranking of respective PTs for the Only HCP group in the 2009–2015 period. Tables 3 and 4 in the ESM show the most frequently reported terms for all categories of primary sources in the pre- and post-legislation period.

For the totality of the observed 2009–2015 period, the most frequently reported reactions for the Only Patient and the Only HCP groups overlapped substantially (13 of 20).

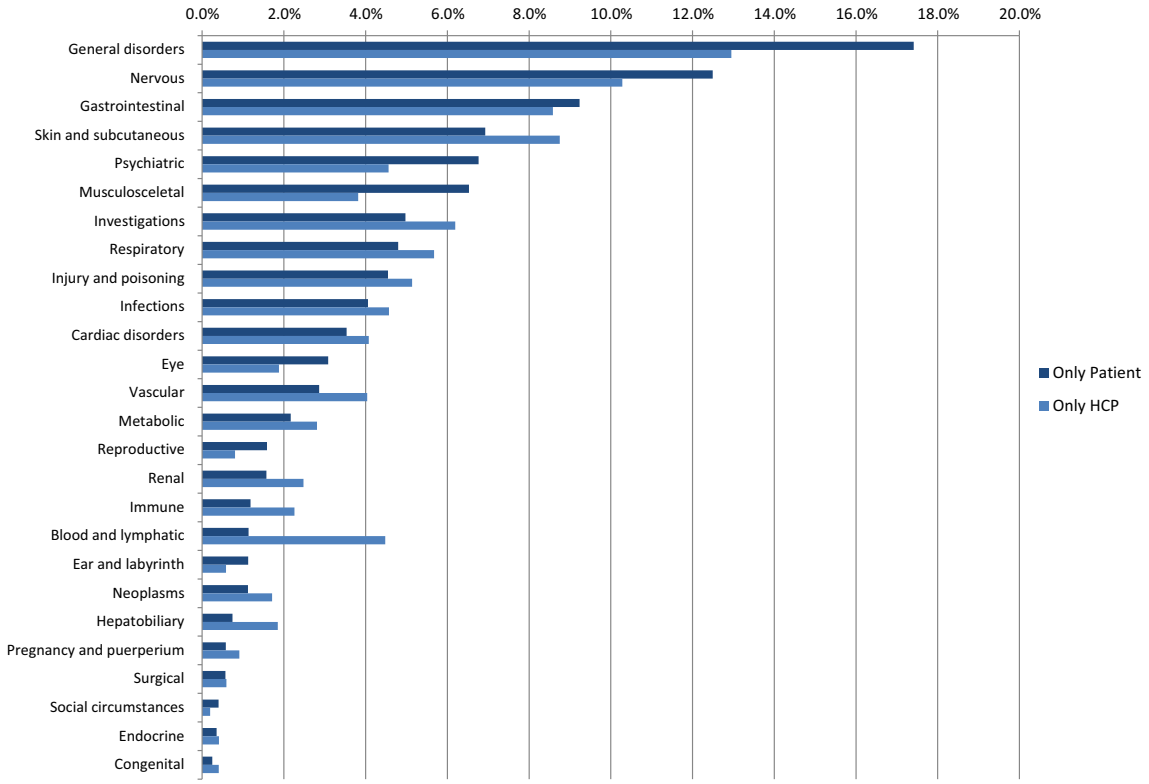


Fig. 7 System Organ Classes ranked by the most frequently reported in Only Patient group between July 2009 and July 2015. *HCP* healthcare professional

Fig. 8 The likelihood of adverse drug reaction reporting by System Organ Class (SOC)—expressed as relative risks for Only Patient compared with Only Healthcare Professional (HCP)

Table 3 Top 20 reported Preferred Terms by Only Patient in the July 2009–July 2015 period

Reaction (MedDRA Preferred Term)	Rank	Only Patient (*N* ICSRs)	Rank	Only HCP (*N* ICSRs)
Headache	1	12,074	9	29,982
Fatigue	2	11,681	16	22,153
Nausea	3	10,030	2	43,336
Dizziness	4	9217	12	25,308
Pyrexia	5	9066	1	55,114
Dyspnoea	6	6629	3	42,912
Diarrhoea	7	6465	6	33,120
Drug ineffective	8	6366	11	26,761
Vomiting	9	5982	4	39,853
Malaise	10	5843	13	25,211
Myalgia	11	5834	28	15,389
Palpitations	12	4815	74	7488
Pruritus	13	4640	7	33,095
Arthralgia	14	4608	37	13,170
Pain in extremity	15	4046	45	11,375
Rash	16	3973	5	33,678
Pain	17	3921	34	13,461
Insomnia	18	3875	99	6446
Hyperhidrosis	19	3755	48	11,014
Asthenia	20	3614	18	19,923

HCP healthcare professional, *ICSR* individual case safety report, *MedDRA* Medical Dictionary for Regulatory Activities

Seven reactions were not among the top 20 reactions most frequently reported by Only HCPs but were included in the top 20 reported by Only Patients: myalgia, palpitations, arthralgia, pain in extremity, pain, insomnia, hyperhidrosis. The majority of injection site reaction-related PTs ranked higher in the Only Patient group than in the Only HCP group (exceptions were injection-site oedema and injection-site abscess). In contrast, urticaria, thrombocytopenia, and hypotension ranked rather low among patient reports (51st, 152nd, 101st, respectively) and high among HCPs reports (8th, 15th, 17th, respectively).

High RRs were observed for PTs that patients could easily identify themselves. This broadly confirmed the conclusions of other studies, which found that patient reports note the effects of ADRs on their lives more often than do HCP reports [15]. Some of these include nicotine dependence (RR 13.45), heart sounds abnormal (RR 10.95), gluten sensitivity (RR 10.45), loss of libido (RR 9.15), or simply patients indicating a decrease in their quality of life (RR 5.83).

Patients were relatively more likely than HCPs to report drug inefficacy. Although, in absolute terms, HCPs reported drugs being ineffective over four times more than the Only patient group (26,761 vs. 6366, respectively), the statistically significant RR of 1.44 (95% confidence interval [CI] 1.41–1.48) might indicate patients' higher motivation to report drug inefficacy. The PT 'drug ineffective' ranked as the 12th most frequently reported PT by patients and only the 78th most frequently reported among HCPs.

As expected, HCPs were more likely than patients to report laboratory findings, such as hyponatraemia (RR 0.12), acute kidney injury (RR 0.15), international normalised ratio increased (RR 0.15), neutropenia (RR 0.17), leukopenia (RR 0.18), and thrombocytopenia (RR 0.18).

4.6 Number of Reactions and Substances on an Individual Case Safety Report

The mean number of reactions per report increased slightly in the Only Patient group after the new legislation (from 3.11 to 3.33).

On average, patients tended to report more reactions per ICSR than did HCPs (Table 4). HCPs reported fewer terms (from 2.49 pre-legislation to 2.45 after the new legislation). As the median number of reactions per report in all observed groups remained the same ($N = 2$), the average was likely driven more by the outliers in all the groups with a very high number of reactions.

Of note, the reports that included a lawyer as a primary source stood out, as the median number of reactions per report was three times higher at a median of six PTs than on the patient or HCP reports (median 2).

Although rare extreme cases have a very high number of suspect substances, on average all reports in EV contain no more than one to two suspect drugs (median 1), and the new legislation did not appear to make a significant change in this regard (Table 5).

4.7 Time to Report

We calculated the time taken (in days) to report an ADR as the time difference between the date the information was received from the primary source (e.g. patient, physician) and the first reaction start date. Before the new legislation,

Table 4 Number of reactions reported on an individual case safety report stratified by primary source

Primary source	All period			Pre legislation			Post legislation		
	ICSRs (*N*)	Mean	Median	ICSRs (*N*)	Mean	Median	ICSRs (*N*)	Mean	Median
Only Patient	180,038	3	2	65,885	3	2	114,153	3	2
Only HCP	1,365,638	2	2	652,816	3	2	712,822	2	2
Legal	6658	8	5	2817	6	3	3841	10	6

HCP healthcare professional, *ICSR* individual case safety report

Table 5 Number of substances reported on an individual case safety report stratified by primary source

Primary source	All period			Pre legislation			Post legislation		
	ICSRs (*N*)	Mean	Median	ICSRs (*N*)	Mean	Median	ICSRs (*N*)	Mean	Median
Only Patient	180,038	1	1	65,885	1	1	114,153	1	1
Only HCP	1,365,638	2	1	652,816	2	1	712,822	2	1
Legal	6658	2	1	2817	2	1	3841	2	1

HCP healthcare professional, *ICSR* individual case safety report

Table 6 Median time to report an adverse drug reaction in days

Primary source	All period	Pre legislation	Post legislation
Only Patient	26	18	32
Only HCP	34	37	31
Legal	607	610	606

HCP healthcare professional

the Only Patient group took a median of 18 days to report an ADR, whereas the median after the new legislation exceeded 1 month (32 days). At the same time, in the Only HCP group, the median time to report was reduced by almost 1 week (from 36 days before to 31 days after the new legislation; Table 6). Changes in the time to report for Only Patient and Only HCP were statistically significant.

Overall, the median time to report an ADR regardless of whether it was the patient or the HCP reporting was 1 month. Legal cases were an outlier, with a median of 607 days taken to report an ADR.

4.8 Reported Indications

Indication for which the medicine was administered is not a mandatory field for a valid ICSR, so not all reports contained this information. As we retrieved over 9000 different terms as reported indications on ICSRs, we grouped the terms according to SOCs and MedDRA High-Level Terms (HLTs) and also presented them as the MedDRA PTs to gain more clarity on the reporting patterns.

4.8.1 Only Patient

Before the implementation of the new legislation, about half (52%) of all patient reports contained indications; this percentage increased to almost three-quarters (73%) post-legislation. Some changes were evident in the Only Patient group in terms of reporting of the indication, i.e. the highest increase in the proportion of reported indications was observed in surgical procedures, infections and endocrine SOCs (the increase for the endocrine SOC was mostly driven by the levothyroxine quality issue [27, 28]). In contrast, eye disorders, metabolism and nutrition disorders, and musculoskeletal SOCs reduced the most in terms of overall proportion of reported indications within the Only Patient group before and after implementation of the legislation (Fig. 6 in the ESM, Fig. 9).

Patients were more than twice as likely as HCPs to report for indications under the following SOCs: endocrine disorders (RR 7.10), reproductive system and breast disorders (RR 2.67), and eye disorders (RR 2.09). For a complete list, see Fig. 10.

The very high RR for endocrine disorders was mostly attributable to the excess patient reports that arose in response to a product quality issue with levothyroxine; this was visible when the indications were analysed at the MedDRA HLT level (Fig. 8 in the ESM). Furthermore, although HCPs were generally (SOC level) more likely to report psychiatric indications, patients were more likely to be the reporter than HCPs for certain psychiatric indications such as panic attacks and stress disorders (Fig. 8 in the ESM).

4.8.2 Only HCPs

The magnitude of changes observed in the Only Patient group in terms of reporting patterns for indications were not observed in the Only HCP group; however, the proportion of reported indications did increase for the neoplasms and respiratory SOCs. This is not unexpected given the number of newly authorized medicines in oncology.[4] Similar to the Only Patient group, the Only HCP group also more frequently reported indications after the new legislation; the percentage of ICSRs with a reported indication increased from 60% before to 74% after the new legislation.

The Only HCP group were more likely than the Only Patient group to report ADRs for medicines administered for indications belonging to blood and lymphatic system disorders (RR 0.29); neoplasms benign, malignant and unspecified (including cysts and polyps) (RR 0.39); hepatobiliary disorders (RR 0.46); and cardiac disorders (RR 0.51). See Fig. 10 for a complete list.

Table 7 shows the most frequently reported indications by Only Patient by PT, and Figures 6 and 7 in the ESM show the proportions of indications classified by SOCs among the Only Patient and Only HCP groups pre- and post-legislation.

4.9 Substance

The results for the substances most frequently reported by the Only Patient group were in line with results for the most frequently reported indications. Analysis showed that immunisation against the pandemic influenza A (H1N1) 2009 virus had a substantial impact on patient reports in the pre-legislation period. For instance, as noted in Sect. 4.8.1, thyroid conditions were over-represented given the epidemiology of thyroid diseases, and the most likely reason for this was the change of packaging in one member state; levothyroxine was the second most frequent medicine reported by the Only Patient group in the post-legislation period (3.4%) but only the 35th most reported before the

[4] The highest proportion of newly authorised medicines in the EU were oncology products. In the 10-year period between July 2006 and July 2016, 23% of all new medicines authorisations in the EU were oncology medicines, followed by antiinfectives and nervous system medicines, accounting for 14% of authorisations.

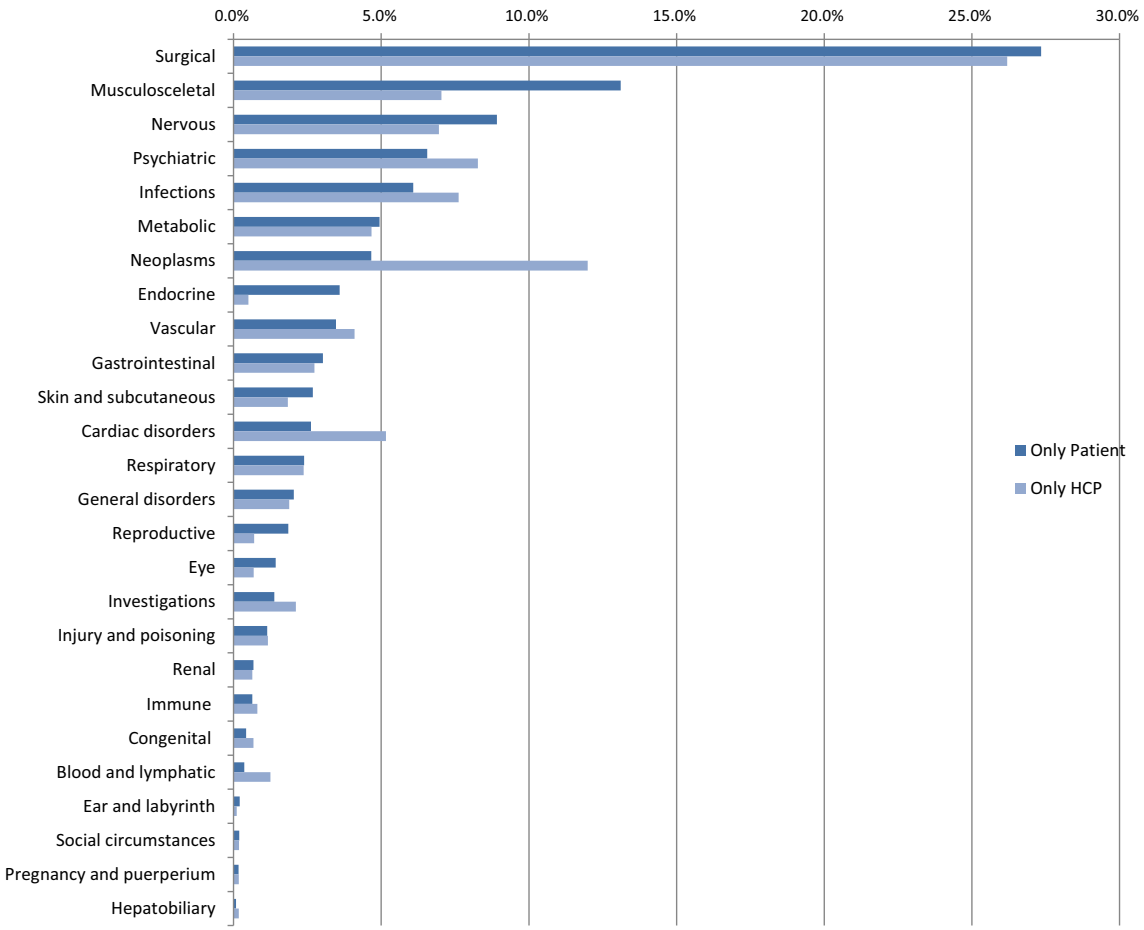


Fig. 9 Reported indications on individual case safety reports for Only Patient and Only Healthcare Professional (HCP) categories between July 2009 and July 2015. Reported terms (indications) were grouped according to System Organ Class. For figures presenting pre- and post-legislation periods per System Organ Class see the Electronic Supplementary Material

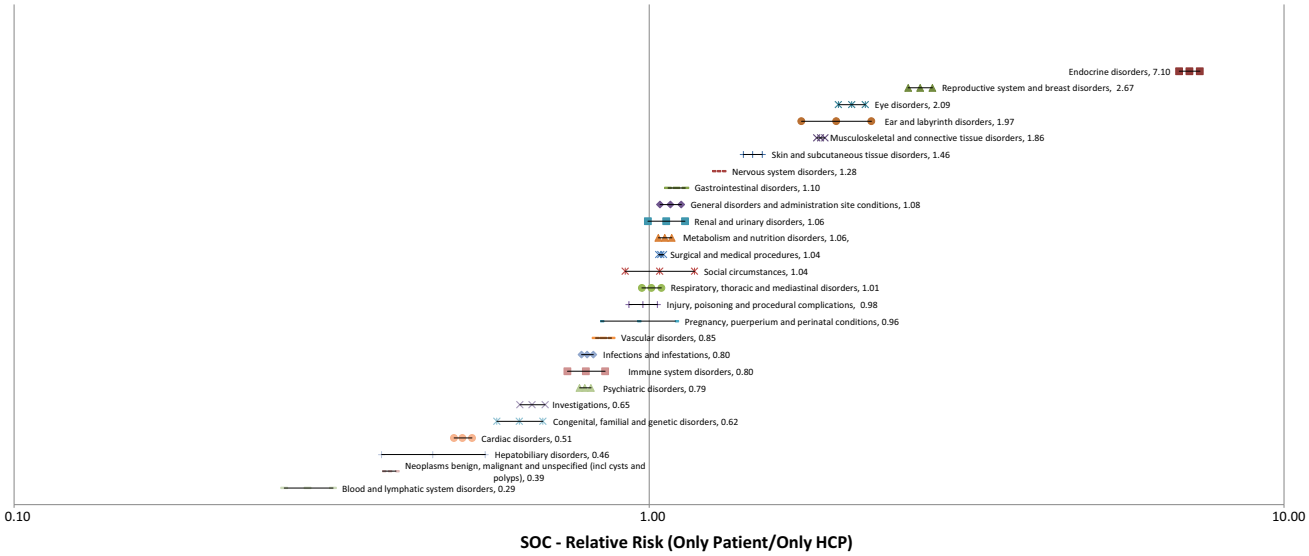


Fig. 10 The likelihood of reporting indications by System Organ Class (SOC) between July 2009 and July 2015—expressed as relative risks for Only Patient compared with Only Healthcare Professional (HCP)

Table 7 Fifty most frequently reported indications by Only Patient according to the number of reports. Reported terms (indications) were grouped according to Preferred Terms

Rank	Indication (MedDRA PT)	Only Patient (*N* ICSRs)	Only HCP (*N* ICSRs)	Risk ratio Only Patient/only HCP)
1	Product used for unknown indication	11,774	85,815	0.97
2	Immunisation	9693	68,477	1.01
3	Rheumatoid arthritis	6480	24,434	1.88
4	Prophylaxis	5162	40,220	0.91
5	Hypertension	3687	29,650	0.88
6	Osteoporosis	3611	11,984	2.14
7	Multiple sclerosis	3552	15,477	1.63
8	Depression	3427	20,015	1.22
9	Contraception	3013	12,793	1.67
10	Hypothyroidism	2805	1054	18.90
11	Parkinson's disease	2187	9047	1.72
12	Diabetes mellitus	2110	11,852	1.26
13	Ankylosing spondylitis	1992	5123	2.76
14	Atrial fibrillation	1912	36,008	0.38
15	Psoriatic arthropathy	1759	5189	2.41
16	Type 2 diabetes mellitus	1751	15,365	0.81
17	Smoking cessation therapy	1695	6797	1.77
18	Psoriasis	1328	9108	1.04
19	Epilepsy	1252	11,367	0.78
20	Pain	1244	10,371	0.85
21	Hypercholesterolaemia	1205	7300	1.17
22	Crohn's disease	1204	9825	0.87
23	Neuralgia	1104	3020	2.60
24	Acne	1035	2912	2.52
25	Breast cancer	986	14,401	0.49
26	Anxiety	932	3475	1.90
27	Thyroid disorder	920	178	36.71
28	Asthma	910	5912	1.09
29	Age-related macular degeneration	867	1946	3.16
30	Type 1 diabetes mellitus	841	2070	2.89
31	Cerebrovascular accident prophylaxis	817	7249	0.80
32	Urinary tract infection	814	6219	0.93
33	Back pain	785	6380	0.87
34	Chronic obstructive pulmonary disease	652	3846	1.20
35	Influenza immunisation	618	3781	1.16
36	Migraine	609	2076	2.08
37	Erectile dysfunction	567	1147	3.51
38	Bronchitis	565	5059	0.79
39	Oral contraception	540	2384	1.61
40	Autoimmune thyroiditis	507	70	51.44
41	Restless legs syndrome	502	1289	2.77
42	Off-label use	498	2169	1.63
43	Osteoporosis postmenopausal	471	2084	1.61
44	Attention deficit/hyperactivity disorder	470	3022	1.10
45	Insomnia	465	2349	1.41
46	Sleep disorder	461	1486	2.20
47	Glaucoma	441	1338	2.34

Table 7 continued

Rank	Indication (MedDRA PT)	Only Patient (*N* ICSRs)	Only HCP (*N* ICSRs)	Risk ratio Only Patient/only HCP)
48	Arthralgia	441	3741	0.84
49	Schizophrenia	437	32,088	0.10
50	Bipolar disorder	434	3542	0.87

HCP healthcare professional, *ICSR* individual case safety report, *MedDRA* Medical Dictionary for Regulatory Activities, *PT* Preferred Term

legislation. Another outlier in the Only Patient group, both pre-legislation and especially in the post-legislation period, was etanercept.

In the Only HCP group, the greatest outlier was rivaroxaban, which was ranked as the 117th most reported medicine before the legislation and as the second most frequently reported medicine post legislation, probably owing to increased exposure in the post-approval years.

Figures 11 and 12 present the 20 most frequently reported active substances and vaccines in the Only Patient and Only HCP groups for the mid-2009 to mid-2015 period.

The reported active substances and vaccines were grouped according to level 1 (anatomical main group) of the Anatomical Therapeutic Chemical (ATC) classification system [29], and the RR for the Only Patient group was calculated relative to the Only HCP group.

The Only Patient group was more likely to report ADRs for medicines belonging to the following ATC groups (statistically significant RRs): systemic hormonal preparations, excluding sex hormones and insulins; genitourinary system and sex hormones; respiratory system; antiparasitic products; insecticides and repellents; sensory organs; dermatologicals; alimentary tract and metabolism; and antiinfectives for systemic use (Fig. 13).

5 Discussion

Patient reporting to EV rose over the whole 6-year period observed, both in terms of numbers and in the proportion of patient reports compared with HCP reports. The rate of increase in patient reports was much higher than that of

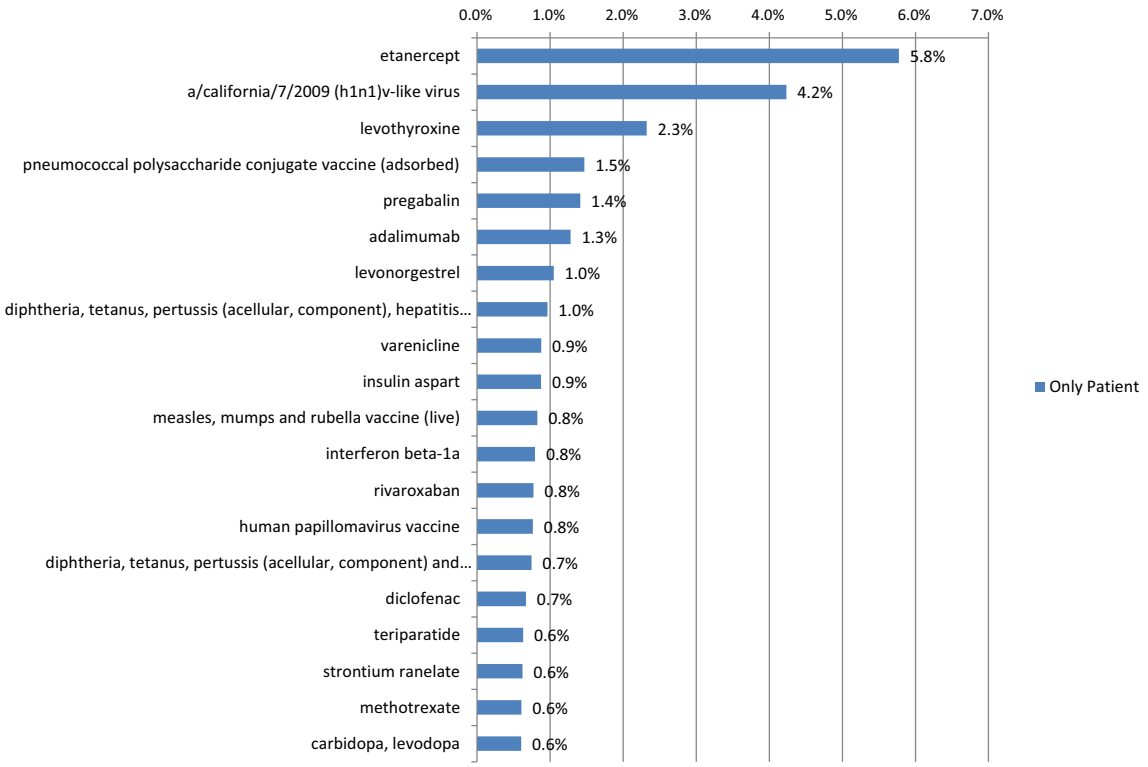


Fig. 11 Top 20 most frequently reported substances by Only Patient for the July 2009–July 2015 period

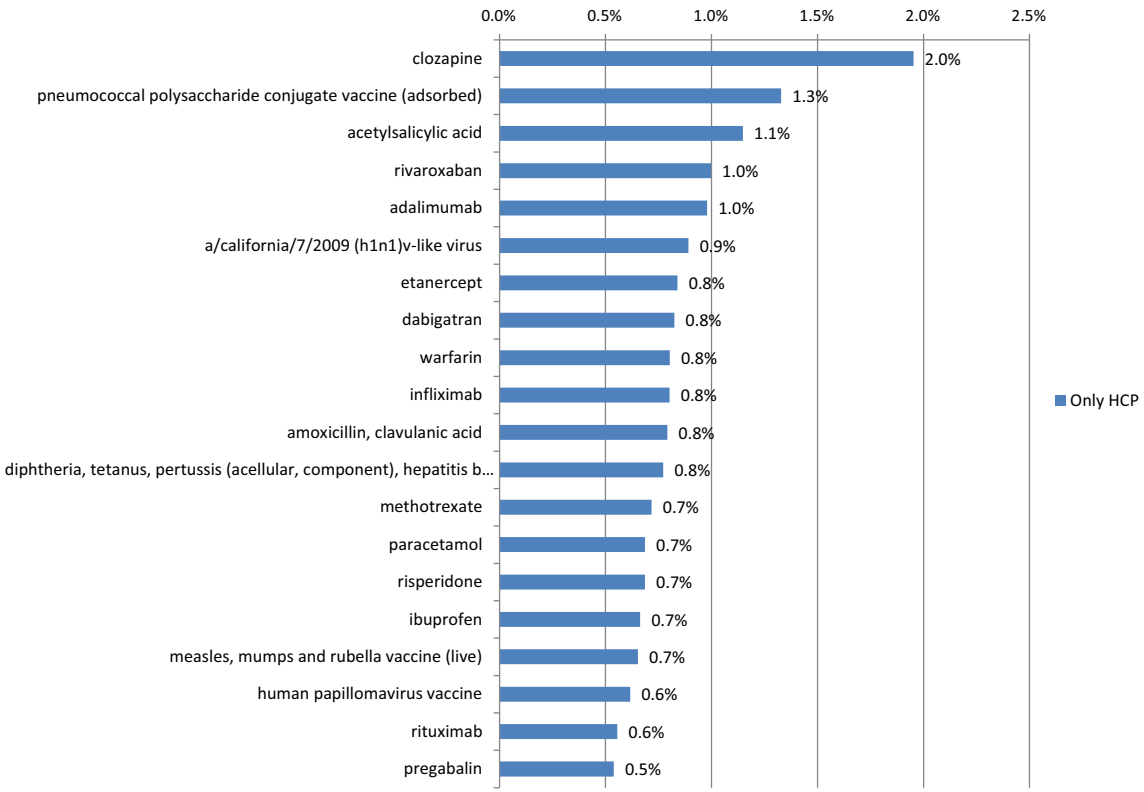


Fig. 12 Top 20 most frequently reported substances by Only Healthcare Professional (HCP) for the July 2009–July 2015 period

HCP reports and all spontaneous EV reports for all observed periods. This increase was expected given the initially low numbers of patient reports compared with HCP reports. The 3-yearly growth rates described should be interpreted with caution as 3 years is not long enough to allow firm conclusions to be drawn; however, the number of patient reports is expected to continue to grow relative to HCP reports as the proportion of reports from the many member states who submit fairly low numbers of patient reports to EV has the potential to increase, and the starting numbers are low compared with HCP reports. The Netherlands stand out, not only because of the very high number of patient reports per million inhabitants but also because patients are starting to report more often than HCPs in absolute numbers (Fig. 1 in the ESM).

We observed a statistically significant increase in the number of serious patient reports from the Only Patient group after the implementation of the new legislation as compared with the 3-year period before ($p < 0.01$). As explained in Sect. 4, these results should be interpreted with caution as the MAHs almost exclusively sent serious reports in the post-legislation period, and their reports comprise two-thirds of the Only Patient reports in that period. Furthermore, the impact of patient support programmes (PSPs), which are organised systems of data collection as opposed to spontaneous reporting, must be considered a possible source of bias because we could not automatically separate PSP reports from 'purely' spontaneous reports to EV. If we consider a portion of MAH reports a proxy for PSP reports (which are mostly serious), then the explanation for the increase in seriousness of Only Patient reports becomes more clear. However, taking into account all of the above, the results regarding seriousness are very difficult to interpret.

Our results show that 13 of the 20 PTs most frequently reported by patients and HCPs and the top three SOCs are identical. In terms of PTs most frequently reported by patients, our findings mostly align with other research, with the difference being that the yellow card study [15] found patients reporting more psychiatric PTs in the top 20 (e.g. anxiety, depression, suicidal ideation), which was not seen in EV. As expected, HCPs reported more PTs belonging to the Investigations SOC, whereas patients reported more in general disorders and administration-site conditions SOCs. Patients seemed to be more motivated than HCPs to report drug ineffectiveness. This observation warrants further analysis for signal detection purposes. As outlined in Sect. 4, it seems that patient reports more often listed reactions that affect patients' quality of life than do HCP reports. However, this study was not designed to test this hypothesis, and an in-depth qualitative analysis was not performed.

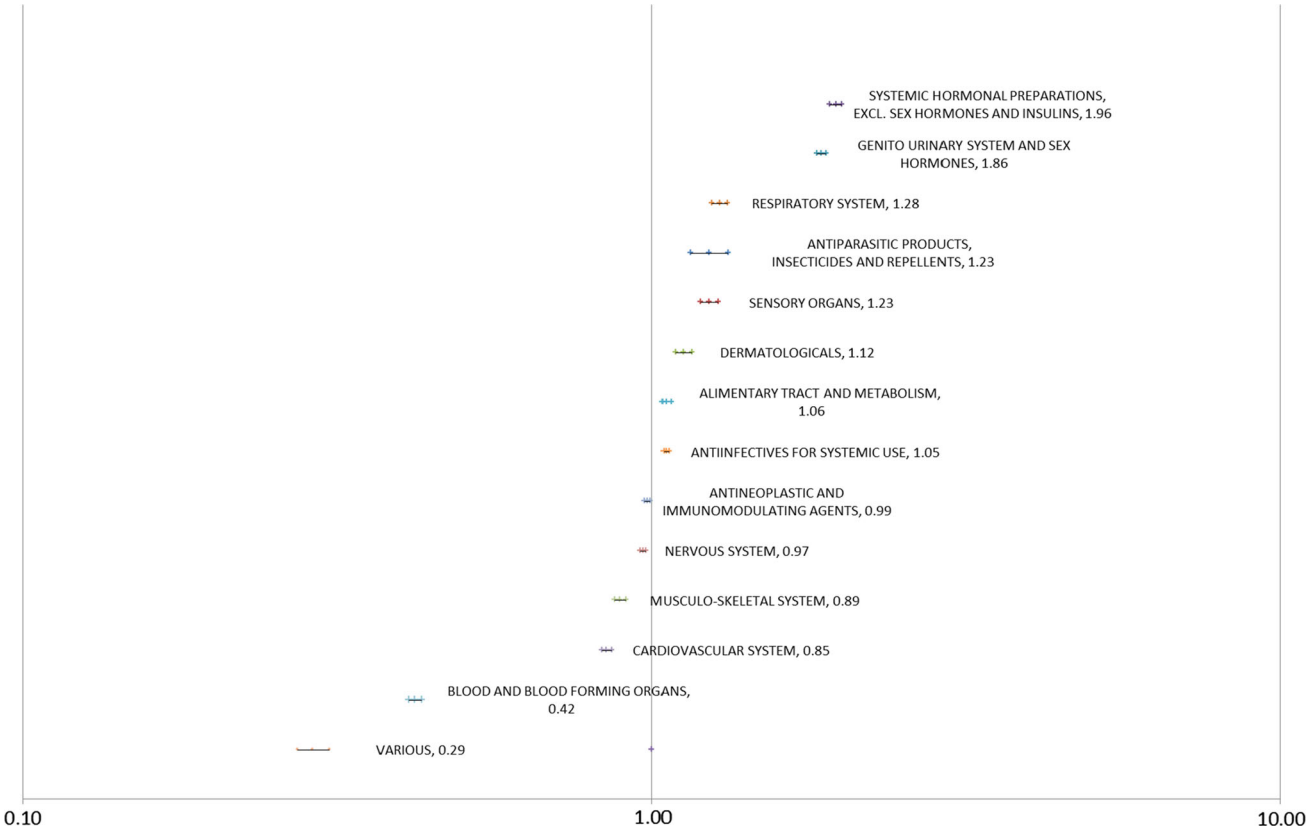


Fig. 13 Anatomical Therapeutic Chemical level 1 (anatomical main group) and the likelihood of reporting an adverse drug reaction by Only Patient and Only Healthcare Professional expressed as relative risk, where the Only healthcare professional group was used as a reference category

Some of the differences between the pre- and post-legislation period in the terms reported by patients were primarily driven not by the legislation but instead by actual situations with diseases and medicines before and after 2012. The H1N1 influenza pandemic caused a spike in the reporting of injection-related reactions in the pre-legislation period (i.e. injection-site pain, injection-site erythema and hyperpyrexia), and the product quality issue with levothyroxine increased the reporting of quality-related terms (product quality issue) and likely thyroid-driven reactions (i.e. palpitations, hyperhidrosis, and asthenia).

When results for reported indications are stratified by the PTs and ranked by the number of reports, they are likely to correlate with the consumption of medicines. As expected, immunization and chronic conditions were highly represented. The results for indications and substances are largely aligned and show that patients were more likely than HCPs to report for genitourinary, hormonal and reproductive indications (2009–2015 period). This pattern of patient reporting could be due to several not necessarily mutually exclusive reasons. One possible explanation is that patients avoid contacting the physician for discretion reasons, as most of these indications concern vaginal/menopausal and prostatic/erection indications. Another possible explanation is that these indications are also related to the use of hormonal contraceptives, a group of medicines that is widely used and relatively over-represented in EV (Table 7 in the ESM) and the safety of which has been assessed in the recent past because of concerns over thromboembolic events and over which substantial media and patient interest was raised. The order of most frequently reported indications did not vary greatly between the observed groups, with the exception of thyroid disorders. This discrepancy was consistent regardless of whether indications were analysed at the SOC, HLT or PT level. Extremely high RRs at the HLT level and the difference in the numbers of reports by patients versus HCPs for thyroid disorders (especially visible when observing the ranking, i.e. hypothyroidism was ranked as the ninth indication on patient reports but only 164th among HCP reports) indicates that this discrepancy might not be due to random variation but rather outstanding issues explained earlier in the text. On the other hand, patients are less likely than HCPs to report ADRs for medicines administered in indications that belong to, for example, blood and lymphatic system disorders; neoplasms benign, malignant and

unspecified (including cysts and polyps); hepatobiliary disorders; cardiac disorders; and congenital familial and genetic disorders SOCs.

While 63% of Only Patient reports to EV were considered serious, only 37% of Only Patient reports contained either an IME or a DME term. As expected, a higher percentage of Only HCP reports contained an IME/DME term compared with patient reports: on average, 82% of HCP reports were serious and 49% of HCP reports contained an IME/DME term. In line with previous observations, the percentage of both serious and IME/DME-containing reports was higher when the patient was not the single primary source (All Patient). A likely reason for this is that serious cases are followed-up by NCAs and MAHs more frequently with HCPs, and this might also result in additional terms on the report that are serious and probably more often part of IME/DME lists.

We observed an increase in the level of populating some important fields on the ICSRs, particularly the indication (average completeness of indication before and after the legislation, 60 and 75%, respectively). However, the completeness of reports in EV (measuring the level of population of all relevant fields on an ICSR) was not within the scope of this study, and its impact on signal detection is an area for future research. This study provides a description of the EU patient reports over the period of 6 years between mid-2009 and mid-2015. It reveals trends in reporting rates and similarities to and differences from HCP reporting. The study does not definitively establish the role of patient reporting but does add to the growing literature. We consider that further analysis of the impact of patient reports on statistical measures of disproportionality, of actual signals validated by regulators, and of qualitative differences and their contribution to signal evaluation will further contribute. Systematic differences in the focus of patient reports and that of HCP reports might suggest that subgroup or stratified analyses should be conducted. Furthermore, because of the specificities of orphan diseases, a dedicated study on patient ADR reporting could prove useful.

This study relied on spontaneous reporting data, and the limitations inherent to spontaneous reporting are applicable.

6 Conclusions

Overall, patient reporting increased after the implementation of the new pharmacovigilance legislation. While patient reporting is well established in some countries, the potential for further increases in the future remains high. Other studies have shown that patient reports complement HCP reporting, which is in line with our results. The results of this study show that 13 of the 20 most frequently reported PTs by patients and HCPs are identical, an important and interesting similarity between HCP and patient reports. As regards the differences, fewer laboratory results and relatively more adverse events affecting patients' everyday life in patient reports than in HCP reports is broadly in line with other studies. Patients are more likely to report genitourinary, hormonal and reproductive indications than are HCPs likely because of discretion issues, which could imply that patient reporting could be a means of communication about drug safety concerns that otherwise would not be flagged. Sharing the results with NCAs and patient associations (i.e. about the substances and indications that are and are not reported) can inform training and awareness on patient reporting. At member states level, the findings could inform targeted campaigns regarding how to report ADRs. At the patient organizations level, the results of this study could supplement the curriculum provided by patient initiatives such as The European Patients' Academy on Therapeutic Innovation (EUPATI) to better inform patients and strengthen patient involvement in ADR reporting. Furthermore, these findings could be considered for any future updates to the EV and EMA ADR reporting websites. This was a benchmarking descriptive study of EV reports, and the overall impact of patient reporting on signal detection should be assessed in a dedicated study.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this study.

Conflict of interest Marin Banovac, Gianmario Candore, Jim Slattery, Francois Houÿez, David Haerry, Georgy Genov, and Peter Arlett have no conflicts of interest that are directly relevant to the content of this study.

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