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ORIGINAL RESEARCH ARTICLE

Adverse Drug Reaction Reporting by Patients: An Overview of Fifty Countries

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Abstract
Background The modalities and contributions to drug safety of patient adverse drug reaction reporting systems in 50 countries have been reviewed and analysed.
Methods The means made available by National Health Competent Authorities (NCAs) for patients to report drug side effects were compared through literature review and questionnaire.
Results Among the 50 countries included in this study, we found that direct patient reporting systems exist in 44 countries and represent 9 % of total reports, the rest coming from healthcare professionals. Australia was the first, in 1964, and the United States has the system in which patients are the most involved. A total of 27 countries have a patient-specific reporting form, and 31 countries provide a form to complete online. In order to help patients, four countries constrain the description of the reaction and 12 constrain the choice of drug on the reporting form. Most of the surveyed countries request the patient's medical history (30 countries) and concomitant therapies (41 countries). The total number of fields per form ranges from 6 to 59, with a mean of 36 items.
Conclusions Most of the surveyed countries have implemented a patient adverse drug reaction reporting system. From this study, it seems that an online reporting form increases the rate of reporting. Currently, many different forms exist worldwide; these should be harmonized by considering the strengths and weaknesses of all existing forms. But above all, to increase the number of reports, each country should promote NCA-initiated adverse drug reactions reporting systems.

Key Points

Most of the countries studied have set up a system for patient reporting of adverse drug reactions, mainly via completion of an online form

17 countries started the patient reporting system in 2012–2013

Systems for patient reporting of adverse drug reactions are diverse

The average patient:healthcare professional ratio for adverse drug reaction reports was around 0.10

1 Background

1.1 Definition and European Regulation

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem." The new European pharmacovigilance legislation (Directive 2010/84/EU) [1, 2] introduced a new culture of pharmacovigilance and proposed changes that will enhance drug safety in Europe. Pharmacovigilance is mainly based on

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notifications from healthcare professionals but now must also take into account spontaneous reporting from patients. The legislation states that the European Medicines Agency (EMA) should develop standardized and structured electronic forms for both healthcare professionals and patients to report suspected adverse drug reactions [3], and that each member state shall record all suspected adverse reactions that occur on its territory and that are brought to its attention by healthcare professionals and patients [2].

1.2 Adverse Drug Reaction Reporting by Patients

The benefits of a direct statement ('first hand' reports) were highlighted during the First International Conference of Consumer Reports on Medicines in 2000. It has been widely recognized that involving patients in reporting leads to a broader base of knowledge on drug safety and allows earlier detection of adverse drug reactions [4, 5]. In the Netherlands, no significant difference between adverse drug reports from patients versus healthcare professionals has been shown, and after 3 years of experience, it was concluded that patient reports could significantly contribute to reliable pharmacovigilance [6]. Blenkinsopp et al. [7] compared declarations made by patients in several countries (Australia, Denmark, the Netherlands, Sweden, USA, and Canada). The quality of reports was similar to those of healthcare professionals and, furthermore, patients may be faster than healthcare professionals in reporting adverse drug reactions. Finally, a report from Health Action International mentioned that patients gave a clearer and more detailed description of their adverse effects than did healthcare professionals [8]. In the UK, patient reports helped to highlight safety signals such as varenicline and risk of aggression, and scopolamine and visual hallucinations [9]. Recently, patient adverse drug reactions reporting systems have been studied in 11 countries, and it appeared that, for all studied countries, patient reports are used for signal detection, which confirms the added value of security data provided by patients [10]. Another study showed that patients report symptoms earlier and more frequently than clinicians do and, with interesting information [11]. Finally, it seems that notifications issued from patients are used for signal detection and publication in many countries [12–14]. On a larger scale, in what is called 'web-pharmacovigilance', analysis of online information-seeking of connected patients could also contribute to drug safety surveillance [15]. The Patient-Reported Outcomes Safety Event Reporting consortium (PROSPER) recently established a guideline to structure the collection of patient safety data, and aims to integrate the voice of patients in the drug life cycle [16]. Direct patient reporting may also be considered as an independent system, as some adverse drug reactions can be filtered by healthcare professionals [17]. It has also been noted that adverse drug reaction reporting by patients offers more advantages than disadvantages. Possible disadvantages include that the patient reporting system can be used by lobby groups or can generate reports that duplicate those of healthcare professionals. Duplicates will overload databases and more importantly, will create additional noise, interfering with safety signal detection.

Several studies have investigated the reasons why patients report adverse drug reactions: altruistic motives came first, with the feeling that their declaration will lead to more research and knowledge on drugs but also the desire to disclose the reaction to other patients. Personal reasons were also evoked; for instance, the wish for patients to have more information about their own adverse drug reaction, or the feeling of being concerned by the potentially causal relationship between adverse drug reaction and medication. Other reasons given for reporting adverse drug reactions are the severity or seriousness of the event and that patients are not satisfied with the information or the care provided by their healthcare professional [18, 19]. Finally, it is worth noting that all countries that have implemented a patient reporting system have observed a positive impact on pharmacovigilance [10].

As the new European pharmacovigilance legislation now allows patients to report potential adverse reactions, it seemed of interest to compare the means made available by National Health Competent Authorities (NCAs) for patients to report such reactions, in Europe but also elsewhere. Thus, a literature review was performed and a questionnaire was sent to 50 countries around the world.

2 Methods

At first, a literature review was conducted (from June 2013 to January 2014; English language only) using the following keywords: 'patients', 'consumer', 'pharmacovigilance', 'adverse drug reactions', and 'adverse drug reaction reporting systems' on the main online databases of medical literature (MEDLINE and EMBASE). Fifty countries that are part of the WHO Programme for International Drug Monitoring [20] were then selected from the five continents, as follows:

- All EU countries in which the new European pharmacovigilance legislation is implemented; plus Norway, Switzerland, and Russia (because of its demographic and economic weight).
- All North American countries (USA, Canada, and Mexico) and five South American countries (Argentina, Brazil, Colombia, Cuba, and Peru) with advanced Pharmacovigilance system [21].
- One country in the Middle East (Israel)

- Three Asian countries (China, India, and Japan) combining demographic and economic weight.
- The two main countries of Oceania (Australia and New Zealand), and
- Five African countries (Algeria, Kenya, Morocco, Nigeria, and South Africa), most of which are long-standing members of the WHO Programme for International Drug Monitoring [22].

A standard questionnaire (Electronic Supplementary Material [ESM] 1) was then sent by email to all NCAs at the same time as the literature and NCA website review was conducted. For each surveyed country, the following information was collected either by questionnaire or by review: NCA contact details; type and content of the side effect reporting form; whether the description of reaction or drug was free text or constrained by either a drop-down list or a drug/medical dictionary; the possibility of reporting other medication(s) and past medical history; and the ease with which the reporting form could be found on the NCA website (number of clicks). We also collected 2012 year-end statistics regarding the number of patient and healthcare professional reports received by the NCA. In terms of questionnaire response, 15 countries responded to the first mailing; reminders were sent to 35 countries, with a response rate of 0.66. Primarily, it was the person in charge of safety (head of vigilance unit, safety assessor, drug safety coordinator, etc.) at the NCA who responded to the questionnaire.

The study (literature review and questionnaires) on patient reporting of adverse drug reactions in 50 countries across the world started in June 2013 and ended in January 2014.

Data collected were listed by surveyed countries in a table but some data were also represented on a world map.

3 Results

The main results regarding the collected information for these 50 countries are presented in Table 1. Among the 50 surveyed-countries, 38 (76 %) replied to our questionnaire. Data for six additional countries (Argentina, Bulgaria, Colombia, Italy, Kenya, and Japan) were retrieved from literature and the website of the NCA concerned. Finally, the data refer to a total of 44 countries. Regarding the patient reporting, those 44 countries enabled patients to directly report adverse drug reactions to their NCA. On average, patients were given the possibility of reporting by 2003; the first country was Australia in 1964, followed 1 year later by New Zealand and Canada (Fig. 1) and the USA in 1969. In the 1990s, three countries (Columbia, Hungary, and Slovenia) started to establish patient reporting. The 2000s saw a dozen countries (Brazil, Croatia, Czech Republic, Denmark, Italy, Malta, Morocco, the Netherlands, Nigeria, Sweden, Switzerland, the UK) implement a patient reporting system. The remaining countries established a patient reporting system in 2012 or 2013 (ESM 2).

3.1 Means of Reporting

Of 44 countries, 27 (61 %) provided bespoke patient forms that differed from those intended to be used by healthcare professionals and were more simple to understand and to complete. For example, in Germany, the patient reporting form was limited to only one page, and the description of the adverse reaction was made easier by a schematic representation of a human body. Moreover, when comparing the specific patient form with that for health professionals, the patient form often used vocabulary that was easier to understand. For example, in the UK, the item "drug indication" was replaced by "reason for taking". Seriousness was requested in both adverse drug reaction forms but was more detailed in the patient form: "Involved or prolonged inpatient hospitalization" was changed to "Bad enough to be admitted to hospital". Moreover, in 39 (89 %) of the 44 countries, patients were assisted by a 'help function', frequently represented by a question mark when completing the form. A total of 31 countries (70 %) offered both online and paper reporting, 11 countries (25 %) offered only paper reporting, and two countries (5 %) offered another way to report based on telephones (in India, patients reported via telephone, and, in Nigeria, text messages were used) (Fig. 2). The adverse drug reaction reporting form was more or less easy to find on the NCA website and, on average, three clicks were sufficient to reach it.

Four countries (9 %), Germany, Spain, the UK, and Japan, constrained the description of the reaction by using a drop-down menu. Denmark, Spain, Greece, Hungary, Norway, the Netherlands, Portugal, the UK, Japan, Israel, New Zealand, and Kenya (27 %) forced the name of the suspected drug by using a semi-automatic data entry or drug dictionary. Medical history was requested by 30 of 44 (68 %) countries, concomitant treatment by 41 countries (93 %), and causality assessment by 42 countries (95 %) for better case analysis.

The total number of items to be completed in the reporting form varied from six (Brazil) to 59 (Austria), with a mean of 36 (standard deviation 12). A total of 30 countries (68 %) imposed mandatory fields on their form, often marked by a red asterisk, with a minimum of three mandatory fields (Canada and Greece) and a maximum of 19 (Denmark, the UK, and Japan). The most asked mandatory fields were the reaction, the name of the suspected drug, the initials of the patient, and the name and address of the reporter. In all countries, the adverse drug reaction was reported either by the patient or by a relative, or via a patients' association. Only three countries (Croatia,

Table 1 Detailed content of the adverse drug reaction patient reporting form by country

Countries	NCA website	Specific patient reporting form	No. of clicks to reach the drug side effect reporting form	Data protection regulation	Medical dictionary for side effect description	Drug dictionary	Medical history field	Concomitant treatment field	Causality assessment field
Algeria	http://www.cnpm.org.dz	No	2	Yes	No	No	Yes	Yes	No
Argentina	http://www.anmat.gov.ar	No	4	Yes	No	No	Yes	Yes	Yes
Australia	http://www.tga.gov.au	Yes	3	Yes	No	No	No	Yes	Yes
Austria	http://www.basg.gv.at	Yes	6	Yes	No	No	Yes	Yes	Yes
Belgium	http://www.fagg-afmps.be	Yes	4	Yes	NA	NA	Yes	Yes	Yes
Brazil	http://www.anvisa.gov.br	Yes	5	Yes	No	No	No	No	Yes
Bulgaria	http://www.bda.bg	Yes	1	Yes	No	No	Yes	Yes	Yes
Canada	http://www.hc-sc.gc.ca	Yes	5	Yes	No	No	Yes	Yes	Yes
China	http://www.sfda.gov.cn	No	2	Yes	No	No	No	No	No
Colombia	http://www.invima.gov.co	No	4	Yes	NA	NA	No	Yes	Yes
Croatia	http://www.almp.hr	Yes	1	Yes	No	No	Yes	Yes	Yes
Cuba	http://www.cecmed.sld.cu	NA	NA	NA	NA	NA	NA	NA	NA
Cyprus	http://www.moh.gov.cy	NA	NA	NA	NA	NA	NA	NA	NA
Czech Republic	http://www.sukl.cz	Yes	4	Yes	No	No	No	Yes	Yes
Denmark	http://www.laegemiddelstyrelsen.dk	Yes	4	Yes	No	Yes	Yes	Yes	Yes
Estonia	http://www.sam.ee	Yes	3	Yes	No	No	Yes	Yes	Yes
Finland	http://www.fimea.fi	No	2	Yes	NA	NA	No	Yes	Yes
France	http://www.ansm.sante.fr	Yes	2	Yes	NA	NA	No	Yes	Yes
Germany	http://www.pei.deet, http://www.bfarm.de	Yes	4	Yes	Yes	No	Yes	Yes	Yes
Greece	http://www.eof.gr	No	1	Yes	No	Yes	Yes	Yes	Yes
Hungary	http://www.ogyi.hu	Yes	3	Yes	No	Yes	Yes	Yes	Yes
India	http://www.cdsco.nic.in	No	NA	Yes	NA	NA	Yes	Yes	Yes
Ireland	http://www.imb.ie	No	2	Yes	No	No	Yes	Yes	Yes
Israel	http://www.health.gov.il	No	3	Yes	No	Yes	Yes	Yes	Yes
Italy	http://www.agenziafarmaco.it	Yes	4	Yes	NA	NA	Yes	Yes	Yes
Japan	http://www.pmda.go.jp	Yes	1	Yes	Yes	Yes	Yes	Yes	Yes
Kenya	http://www.pv.pharmacyboardkenya.org	No	1	Yes	No	Yes	No	Yes	Yes
Latvia	http://www.zva.gov.lv	No	1	Yes	No	No	Yes	Yes	Yes
Lithuania	http://www.vvkt.lt	Yes	2	Yes	NA	NA	Yes	Yes	Yes
Luxembourg	http://www.ms.etat.lu	No	ND	Yes	NA	NA	Yes	Yes	Yes
Malta	http://www.medicinesauthority.gov.mt	Yes	3	Yes	No	No	No	Yes	Yes
Mexico	http://www.cofepris.gob.mx	Yes	4	Yes	No	No	Yes	Yes	Yes
Morocco	http://www.sante.gov.ma	Yes	3	Yes	No	No	No	No	Yes
The Netherlands	http://www.lareb.nl	Yes	2	Yes	No	Yes	No	Yes	Yes
New Zealand	http://www.medsafe.govt.nz	No	4	Yes	No	Yes	Yes	Yes	Yes
Nigeria	http://www.nafdac.gov.ng	Yes	NA	Yes	NA	NA	No	No	Yes

Table 1 continued

Countries	NCA website	Specific patient reporting form	No. of clicks to reach the drug side effect reporting form	Data protection regulation	Medical dictionary for side effect description	Drug dictionary	Medical history field	Concomitant treatment field	Causality assessment field
Norway	http://www.legemiddelverket.no	Yes	3	Yes	No	Yes	Yes	Yes	Yes
Peru	http://www.digemid.minsa.gob.pe	NA	NA	NA	NA	NA	NA	NA	NA
Poland	http://www.urpl.gov.pl	Yes	3	Yes	NA	NA	No	Yes	Yes
Portugal	http://www.infarmed.pt	No	2	Yes	No	Yes	Yes	Yes	Yes
Romania	http://www.anm.ro	NA	NA	NA	NA	NA	NA	NA	NA
Russia	http://www.mednet.ru	NA	NA	NA	NA	NA	NA	NA	NA
Slovakia	http://www.sukl.sk	No	3	Yes	NA	NA	No	Yes	Yes
Slovenia	http://www.jazmp.si	No	3	Yes	NA	NA	Yes	Yes	Yes
South Africa	http://www.doh.gov.za	NA	NA	NA	NA	NA	NA	NA	NA
Spain	http://www.aemps.gob.es	Yes	3	Yes	Yes	Yes	Yes	Yes	Yes
Sweden	http://www.lakemedelsverket.se	Yes	1	Yes	No	No	Yes	Yes	Yes
Switzerland	http://www.swissmedic.ch	No	2	Yes	NA	NA	Yes	Yes	Yes
UK	http://www.mhra.gov.uk	Yes	4	Yes	Yes	Yes	Yes	Yes	Yes
USA	http://www.fda.gov	Yes	3	Yes	No	No	Yes	Yes	Yes

Countries	NCA website	No. of fields to complete in reporting form	Mandatory fields in reporting form	No. of mandatory fields in the reporting form	Online form to complete	No. of total reports received by NCA in 2012	Patient reports (%)	Health professional reports (%)
Algeria	http://www.cnpm.org.dz	26	Yes	6	Yes	ND	ND	ND
Argentina	http://www.anmat.gov.ar	27	Yes	5	Yes	6,546	2.0	98.0
Australia	http://www.tga.gov.au	34	Yes	11	Yes	14,400	3.0	97.0
Austria	http://www.basg.gv.at	59	Yes	13	Yes	5,053	5.0	95.0
Belgium	http://www.fagg-afmps.be	57	No	NA	No	4,601	46.0	54.0
Brazil	http://www.anvisa.gov.br	6	No	NA	Yes	6,067	5.0	95.0
Bulgaria	http://www.bda.bg	27	Yes	7	Yes	461	1.5	98.5
Canada	http://www.hc-sc.gc.ca	39	Yes	3	Yes	30,634	30.5	69.5
China	http://www.sfda.gov.cn	21	Yes	10	Yes	39,306	ND	ND
Colombia	http://www.invima.gov.co	44	No	NA	No	7,252	ND	ND
Croatia	http://www.almp.hr	24	Yes	6	Yes	1,923	2.3	97.7
Cuba	http://www.cecmed.sld.cu	NA	NA	NA	NA	1,556	NA	100.0
Cyprus	http://www.moh.gov.cy	NA	NA	NA	NA	300	NA	100.0
Czech Republic	http://www.sukl.cz	14	Yes	6	Yes	2,167	3.5	96.5
Denmark	http://www.laegemiddelstyrelsen.dk	44	Yes	19	Yes	4,928	34.0	66.0
Estonia	http://www.sam.ee	44	Yes	7	Yes	132	9.0	91.0
Finland	http://www.fimea.fi	28	No	NA	No	1,814	13.9	96.1
France	http://www.ansm.sante.fr	48	No	NA	No	38,296	4.0	96.0

Table 1 continued

Countries	NCA website	No. of fields to complete in reporting form	Mandatory fields in reporting form	No. of mandatory fields in the reporting form	Online form to complete	No. of total reports received by NCA in 2012	Patient reports (%)	Health professional reports (%)
Germany	http://www.pei.deet, http://www.bfarm.de	37	Yes	9	Yes	17,122	3.6	96.4
Greece	http://www.eof.gr	32	Yes	3	Yes	1,180	ND	ND
Hungary	http://www.ogyi.hu	28	Yes	9	Yes	1,641	1.3	98.7
India	http://www.cdsco.nic.in	NA	No	NA	No	12,580	ND	ND
Ireland	http://www.imb.ie	57	Yes	11	Yes	2,784	2.0	98.0
Israel	http://www.health.gov.il	45	Yes	10	Yes	1,800	ND	ND
Italy	http://www.agenziafarmaco.it	56	No	NA	No	21,464	ND	ND
Japan	http://www.pmda.go.jp	45	Yes	19	Yes	5,231	3.8	96.2
Kenya	http://www.pv.pharmacyboardkenya.org	36	Yes	18	Yes	ND	ND	ND
Latvia	http://www.zva.gov.lv	29	Yes	5	Yes	312	1.0	99.0
Lithuania	http://www.vvkt.lt	33	No	NA	No	342	0.0	100.0
Luxembourg	http://www.ms.etat.lu	30	Yes	4	No	ND	ND	ND
Malta	http://www.medicinesauthority.gov.mt	26	No	NA	Yes	300	0.3	99.7
Mexico	http://www.cofepris.gob.mx	39	Yes	6	Yes	19,501	1.0	99.0
Morocco	http://www.sante.gov.ma	19	No	NA	Yes	3,076	10.4	89.6
The Netherlands	http://www.lareb.nl	41	Yes	18	Yes	7,422	35.0	65.0
New Zealand	http://www.medsafe.govt.nz	38	No	NA	Yes	4,253	1.4	82.4
Nigeria	http://www.nafdac.gov.ng	NA	No	NA	No	2,330	1.3	98.7
Norway	http://www.legemiddelverket.no	33	Yes	7	Yes	2,765	6.5	93.5
Peru	http://www.digemid.minsa.gob.pe	NA	NA	NA	NA	2,325	NA	100.0
Poland	http://www.urpl.gov.pl	25	Yes	5	No	1,148	2.3	97.7
Portugal	http://www.infarmed.pt	49	Yes	8	Yes	3,104	1.0	99.0
Romania	http://www.anm.ro	NA	NA	NA	NA	ND	NA	100.0
Russia	http://www.mednet.ru	NA	NA	NA	NA	ND	NA	100.0
Slovakia	http://www.sukl.sk	35	No	NA	No	966	1.8	98.2
Slovenia	http://www.jazmp.si	24	Yes	10	No	849	3.0	96.0
South Africa	http://www.doh.gov.za	NA	NA	NA	NA	ND	NA	100
Spain	http://www.aemps.gob.es	49	Yes	11	Yes	14,000	1.6	98.4
Sweden	http://www.lakemedelsverket.se	40	Yes	7	Yes	5,237	21.0	79.0
Switzerland	http://www.swissmedic.ch	43	No	NA	No	5,913	5.0	95.0
UK	http://www.mhra.gov.uk	53	Yes	19	Yes	236,681	13.0	87.0
USA	http://www.fda.gov	39	Yes	9	Yes	874,116	47.6	52.4

NA not applicable, *NCA* National Health Competent Authority, *ND* not determined

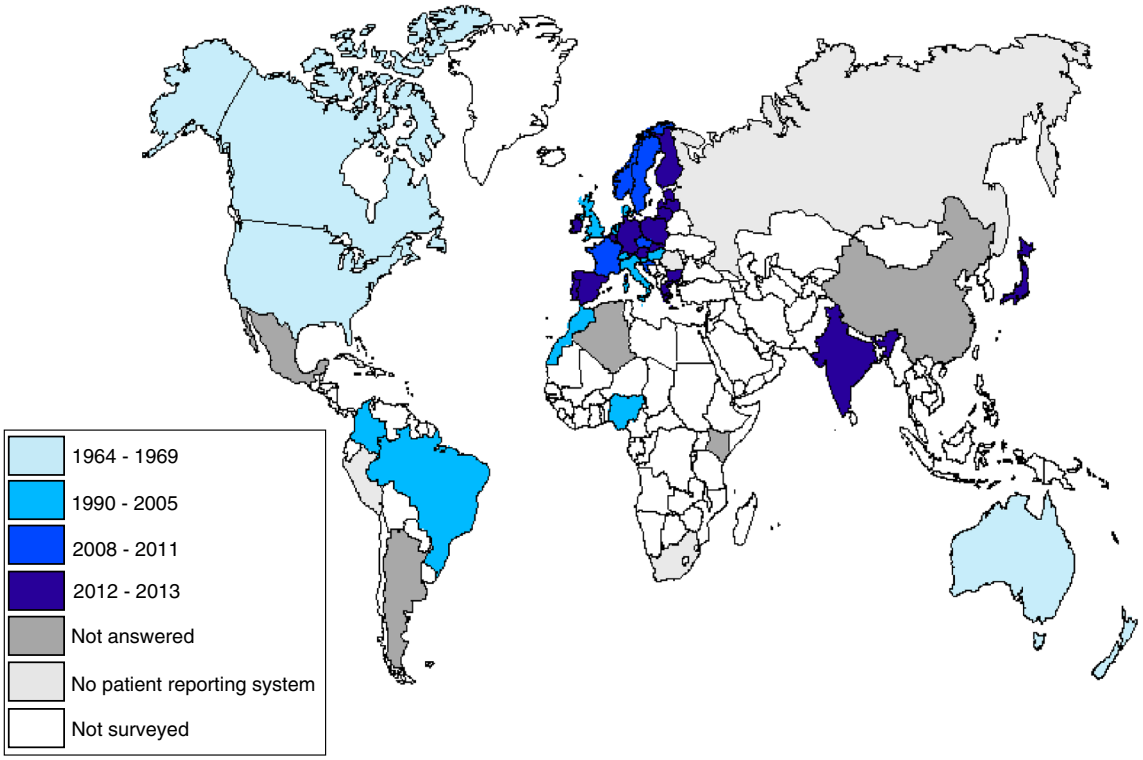

Fig. 1 World map showing the starting date of the direct patient adverse drug reporting in the 50 countries of the study

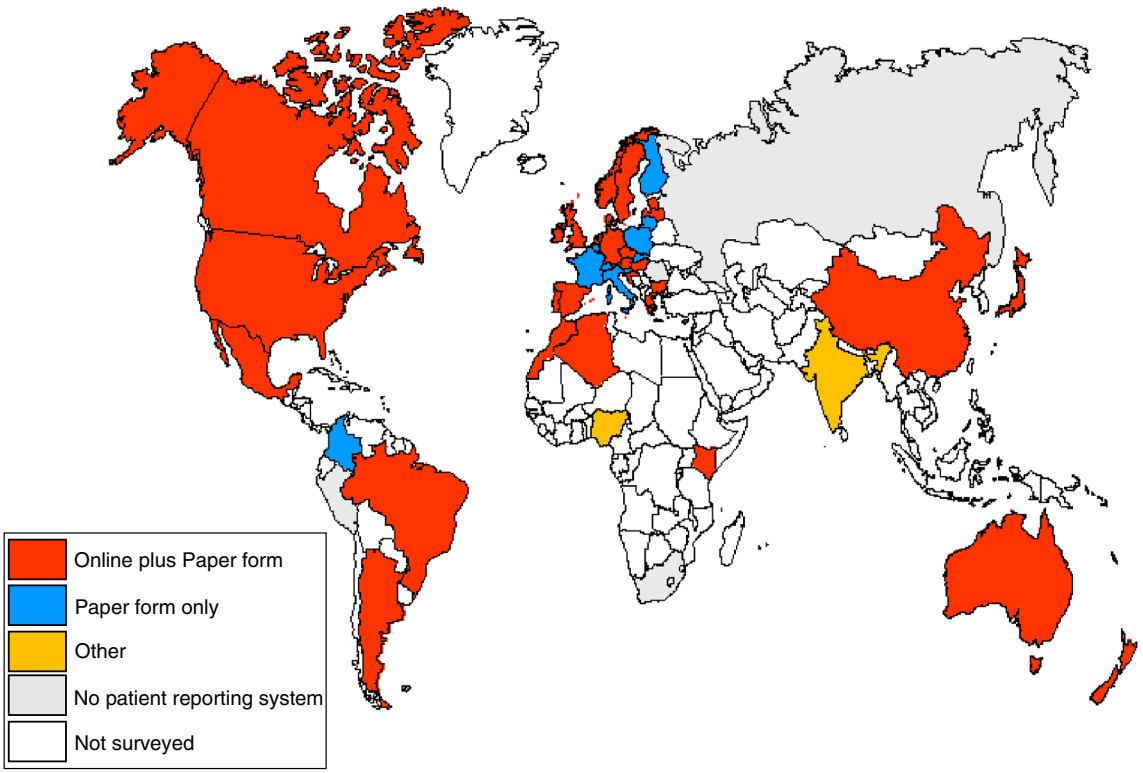

Fig. 2 World map showing the means of adverse drug reaction reporting proposed to patients (online, paperform, other…) in the 50 countries of the study

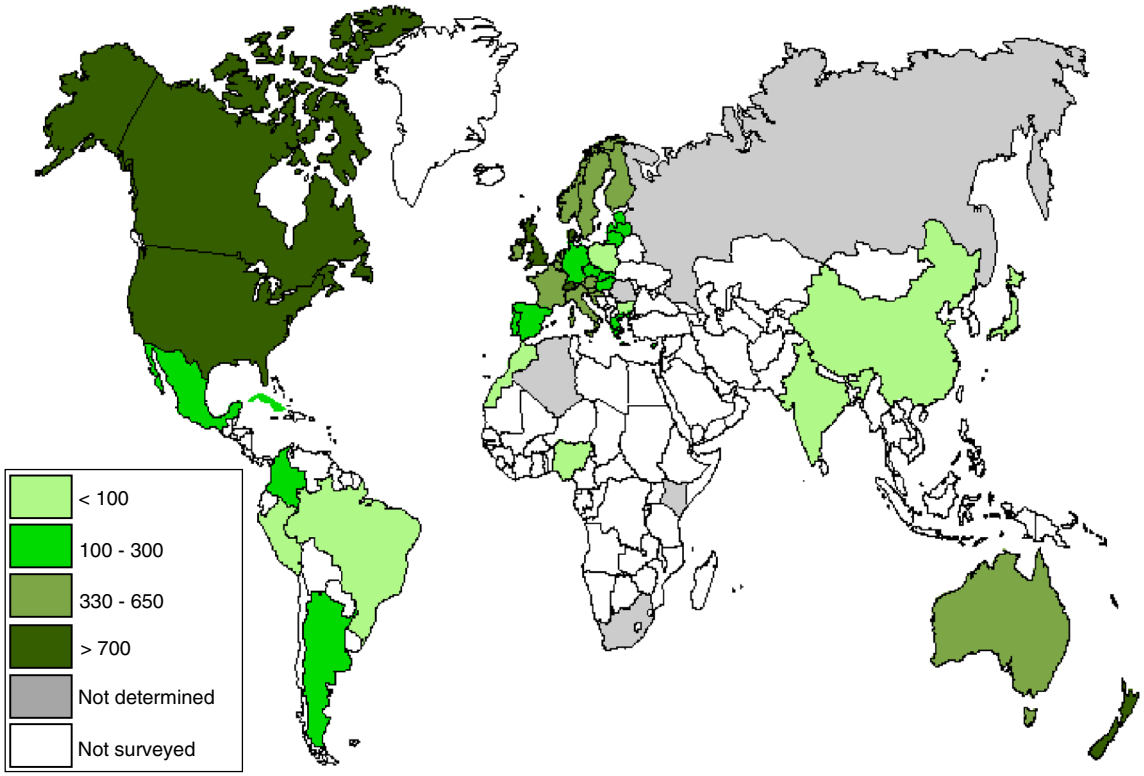

Fig. 3 World map showing the number of adverse drug reaction reports per year per million of inhabitants in the 50 countries of the study

Norway, and Slovenia) asked for the country in which the event occurred (7 %).

Only three countries (Germany, New Zealand, and Kenya) in our study currently offered patients the ability to report serious adverse reactions through the download of an application for mobile devices.

Patients were able to send a follow-up to the NCA in 20 countries (45 %), usually thanks to the worldwide unique identifier of the pharmacovigilance case, which was accessible to patients in 19 countries (43 %). The NCA was able to contact the patient in order to get more information on the case in 37 countries (84 %). In all the 44 countries, the patient adverse drug reaction reporting system is under personal data protection regulation. It was also noted that the national pharmacovigilance database is publicly accessible in eight countries (18 %) (ESM 3).

3.2 Reporting Frequency

The median number of pharmacovigilance reports per year was 3,678, with a minimum of 132 reports per year (Estonia) and a maximum of 874,116 reports per year (USA). We calculated the number of adverse drug reaction reports per year per million inhabitants (Fig. 3): the UK was the highest, with 3,700 adverse drug reaction reports per year per million inhabitants; the USA had approximately 2,700; and the last countries were India and Nigeria, with about ten pharmacovigilance reports per year per million inhabitants (ESM 4).

Among pharmacovigilance reports received by NCAs in 2012, those issued by patients (Fig. 4) represented an average of 9 % (91 % are from healthcare professionals), with the highest patient reporting rates observed in the USA and Belgium (48 and 46 %, respectively) followed by the Netherlands and Denmark (35 and 34 %, respectively). Countries with the lowest rate of patient adverse drug reporting were Mexico, Latvia, Lithuania, Malta, and Portugal, with <1 % of reports coming from patients. Most of these countries have recently implemented a patient reporting system (2012 or 2013).

Patient:healthcare professional reporting ratios were the highest in Northern Europe and North America.

When comparing world maps showing the percentage of adverse drug reaction reporting by patients (Fig. 4) versus the starting date of direct patient reporting (Fig. 1), it seems that the older the reporting system (light blue in Fig. 1), the higher the reporting rate (red in Fig. 4), except in Oceania. Similarly, countries that allow online reporting (red in Fig. 2) have the highest reporting rate (red in Fig. 4).

4 Discussion

Many countries surveyed in this study are, in fact, only starting patient adverse drug reaction reporting (17 of 50 countries began in 2012 or 2013), which could explain the

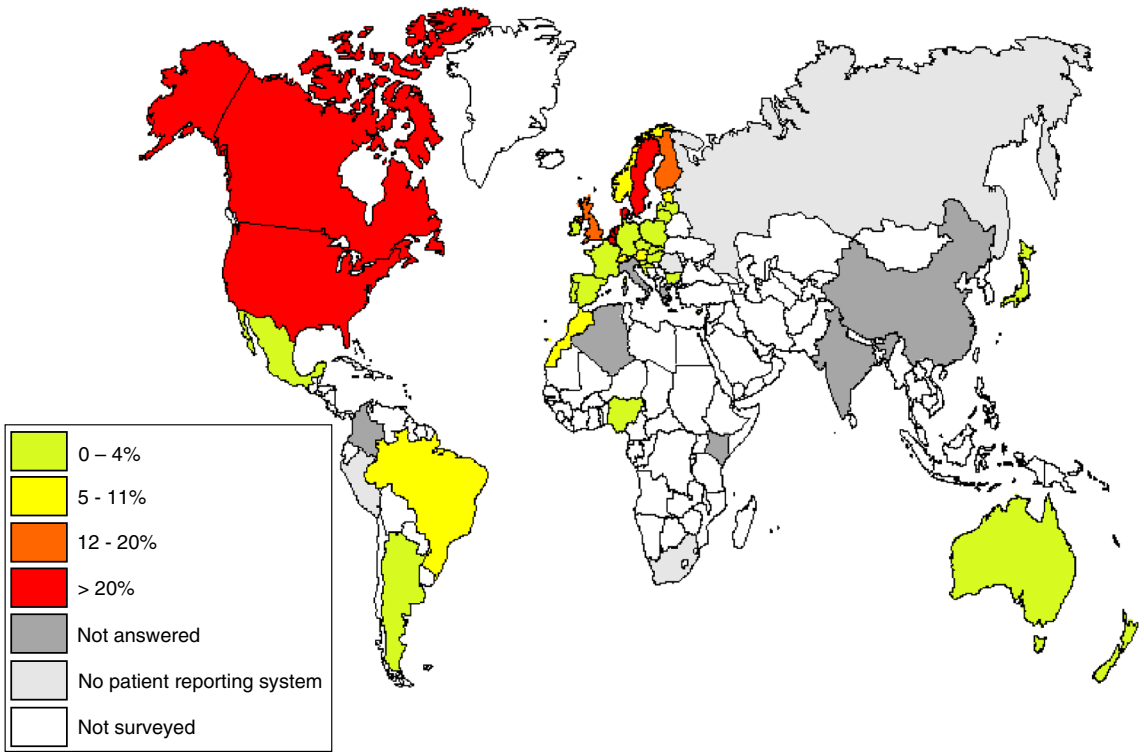

Fig. 4 World map showing the percentage of patient reports versus those of healthcare professional in the 50 countries of the study

low percentage of direct reporting by patients to NCA observed in some countries. In the 2000s, the increase in countries that implemented a patient reporting system might be because regulators were encouraged to include patients in the drug safety process after the Erice declaration [23, 24]. For countries that had authorized the reporting of adverse events by patients for many years, under-reporting might be due to a lack of knowledge by patients about the possibility of reporting adverse drug reactions. According to a study in the UK, only 8.5 % of patients were aware of the 'Yellow card' system [25]. An Australian study performed in 2013 also highlighted this, and the authors concluded that promoting the system and the training of patients can be helpful for increasing the number of reports [26]. For example, in Ireland, when patient reporting was initiated, so too was a campaign displaying leaflets in pharmacies [27].

The results of this study have some limitations as they are based on a questionnaire and literature review and are an instant snapshot reflecting the current situation. Results showed that the rate of reports greatly increases when patients are able to report adverse drug reactions online. However, the forms currently provided by NCAs are all different and there is thus a need for harmonization between the various reporting systems, at least at the European level, an objective that can be achieved with the European project on e-pharmacovigilance [28]. In 2012, Singh and Bhatt [29] compared the forms used by healthcare professionals for adverse drug reaction reporting in 13 countries and proposed a standardized reporting form with all recurring items and items important for case analysis. It seems important that the same work should be conducted for the patient reporting form, for example by the Uppsala Monitoring Centre (international monitoring center dedicated to pharmacovigilance and under the auspices of the WHO). It would be interesting to take the strengths of each national form (e.g. ease of completion by constraining the adverse reaction field with medical dictionary terms and drug names with drop-down menus or help symbols). The harmonized reporting form should be fast to complete and should be online with a matching mobile phone application. Relevant information, such as concomitant medications, past medical history or the concept of dechallenge/rechallenge should not be so far removed.

Efforts are still needed in pharmacovigilance, especially in developing countries, despite the WHO Programme for International Drug Monitoring. In 2010, Olsson et al. [30] conducted a survey of 55 low- and middle-income countries, identifying the challenges and barriers these countries face in promoting pharmacovigilance but also underlying their willingness to encourage patient reporting of adverse drug reactions. In September 2012, Nigeria introduced the PRASCOR system (Pharmacovigilance Rapid Alert System for Consumer Reporting) to allow patients to report

adverse events: an interesting system in a developing country where the mobile phone is more entrenched than the Internet [31]. To declare, patients send a free message to a toll-free phone number, explaining which medication they took and which reaction occurred. They receive an acknowledgment and are then contacted by the NCA within 24 h for more information on their case. The patient can also get advice to avoid further adverse reactions. Another example is the October 2013 establishment by the Indian Pharmacopoeia Commission of a toll-free number giving patients the opportunity to declare their adverse drug reaction across the country.

The opportunity for patients to report drug side effects allows optimization of drug-related risk monitoring, detection of safety signals complementary to those reported by health professionals, and most importantly, the involvement of all health system stakeholders.

5 Conclusions

Of 50 surveyed countries that are part of the WHO Programme for International Drug Monitoring, it appears that 44 have already implemented means of adverse drug reaction reporting by patients. Except for a few countries, reporting by patients began in the 2000s. The most common means implemented by the NCA for patients to report adverse drug reactions is via a paper form coupled with an online form. In terms of reporting frequency, the majority of surveyed countries average fewer than 700 reports per year per million inhabitants. Finally, in 2012, the average patient:healthcare professional ratio for adverse drug reaction reports was around 0.10. From these results, the overall impression that emerges is that the increase of reporting by patients to NCAs, supports the idea of the paradigm shift from physician-centered towards patient-centered in terms of drug safety. More broadly, it also questions the evolution of patient behaviors and their relationship to medicine and scientific progress; the patient is now a demanding and active customer for his/her own health. The benefits of patient contribution to drug safety are now established and are set to increase, particularly with the rapid development of mobile communication media. Patient involvement is now acquired and will eventually help to increase safety understanding, competence, and awareness by the general population.

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