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Exploring sociodemographic and economic factors that promote adverse drug reactions reporting by patients☆

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ABSTRACT

Background: Adverse drug reactions (ADRs) are recognized as a leading cause of morbidity and mortality, and an important cost factor to health systems. Patient reporting of ADRs has emerged as an important topic in recent years but reporting rates are still low in many countries.
Objective: To explore different countries' sociodemographic and economic features as explanatory factors for population ADRs reporting, including the propensity of patients' reporting to pharmacovigilance authorities.
Methods: Cross-sectional observational design. A data set of 42 global sociodemographic and economic factors for 44 countries were retrieved, as to analyse statistical associations between these factors and the patient reporting rate of ADRs. Multivariate logistic regression models were designed to identify the predictive covariables.
Results: Health investment indicators, such as per capita public health expenditure, hospital bed density and under five mortality rate were the relevant factors responsible to discriminate between countries that have higher patient reporting rates.
Conclusions: This study shows that healthcare investment-related factors help explain the propensity of patients to report suspected ADRs, while pharmacovigilance features were not directly associated with higher patient participation in drug safety mechanisms. Although general, these results point a direction in further policy making to improve resources allocation concerning the promotion of patients' participation.

1. Introduction

Adverse drug reactions (ADRs) are recognized as a leading cause of morbidity and mortality, and an important cost factor to health systems in different countries [1]. The economic impact of ADRs is complex and multifactorial [2]. It seldom leads to hospitalization of patients, with corresponding pharmacotherapy problems and increasing costs during their hospital stay [3]. ADRs are among the top ten causes of death in some countries [4]. In the European Union (EU) alone, it is estimated that the total costs are high as €79 billion, causing over 197,000 deaths annually [3].

Pharmacovigilance aims to improve public health and safety in relation to the use of medicines by reducing the substantial burden of disease resulting from ADRs, through better monitoring of medicines in the post-marketing setting [3].

In the past few years there has been a greater focus on patient-reported outcomes. The patient has turned from being a passive receptor of care to become an active player in the management of its own health status [5]. Patient-centeredness and patient safety have emerged as core elements in today's interactive and responsive healthcare systems. Regulators and the pharmaceutical industry are compelled to meet increasing patient expectations and engage in shared decision making [6]. In a survey of eleven countries worldwide authorities reported that engaging the public in pharmacovigilance activities is an important issue [7]. Most countries are nowadays accepting ADR reports from patients [8]. Evidence has been building on the complementary information patients add.

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Patients help in signal detection, reporting new suspected ADRs for different system organ classes and groups of medicines when compared with healthcare professionals (HCPs). Patient reports deliver a more personalized description of the ADRs, providing detailed information on the impact and severity that ADRs cause in daily life [9]. Despite that, patient participation is limited. The level of awareness is still low, an element that could be attributed to the fact that many countries only started accepting patient ADR reports from 2012 and 2013 [10]. Currently, research has been done focusing primarily on patients' individual characteristics and experiences [11–13].

Since the year 2000 the access to medicines has been increasing in many parts of the world. In Africa, Asia and Latin America there has been increased access to prevent and treat communicable diseases like malaria, tuberculosis and HIV/AIDS [14]. In the developed world there has been a shift in the disease burden towards chronic diseases, which require more complicated therapeutic regimens [15]. In many countries, developed or developing, the practice of self-medication is also common [7]. A bigger medicines consumption can bring many prospective benefits, but the probability of harm is also higher. These changes can have an impact on public health, especially if ADRs are not monitored, detected and managed. Especially in lower income countries, patient reporting could have the potential to complement HCP reports and highlight possible drug-related public health issues. More needs to be done to investigate which societal factors can influence patients to report more proactively.

This study aims to explore associations between various sociodemographic and economic factors in different countries of the world, and the reporting of suspected ADRs by patients to national pharmacovigilance authorities. The knowledge generated from this study will help decision making on where to place resources to stimulate patient reporting on a global scale.

2. Methods

The study followed a cross-sectional observational design, with data collection and analysis consisting of three parts: (1) identification of relevant sociodemographic and economic factors, (2) search for and collection of relevant data, and (3) development and application of a statistical model on the dataset.

2.1. Identification of relevant sociodemographic and economic factors

Fifty countries from different geographical areas that participate in the World Health organization (WHO) Programme for International Drug Monitoring were included following previous relevant studies, especially one conducted by Florence Margraff and colleagues [10]. This study presented an exhaustive comparison between 44 countries that have patient reporting (Table 1), with the aim of identifying differences in the pharmacovigilance systems, as well as presenting data about the percentage of how much patient reporting contributes to national pharmacovigilance activities.

Information that could be associated with patient reporting mainly comprised indicators of global public health and economic performance. The selection of relevant factors at this point was based on prior knowledge and theoretical value to address study aims and allowing for further statistical estimations [16]. Here, a total of 42 different factors were possible to identify, comprising demographic, socioeconomic and healthcare related information, mainly resulting from the evaluation of the databases mentioned in the next subheading.

2.2. Data collection

For these 44 countries, data were retrieved from databases maintained by several organizations. These included the United Nations Educational, Scientific and Cultural Organization (UNESCO) Institute of Statistics database, World Health Organization (WHO) WHO Global Health Observatory Data Repository, the Organization for Economic Cooperation and Development (OCDE) Health Statistics, complemented by the Central Intelligence Agency (CIA) World Factbook, and the World Bank Databank on missing data. Information on the desired outcome, i.e. the percentage of population reporting ADRs, was only possible to access for 35 different countries (Table 2).

Data from all relevant factors were extracted, providing a comprehensive summary of the circumstances of the economy and general health status of the considered countries. As the data was retrieved from multiple sources, we adapted and used the principles of data quality described by Brown et al. [17]. The data was checked by two researchers (PI and AC) and disagreement was sorted by consensus. Information was collected for the most recent and comparable year that values were available, falling in 2013, where a minimum number of missing information for each individual country existed, diminishing uncertainty. When data were not available for 2013, a range of +/− 2 years was searched for all countries. If again unavailable, information was searched retrospectively until 2005 for specific factors, addressing all countries for the same time interval (e.g. proportion of births attended by skilled health personnel). The factors were disaggregated by sex and age groups, whenever possible.

2.3. Development and application of the statistical model on the dataset

The raw variables were retrieved to an Excel spreadsheet (Supplementary File 1) and the final dataset was checked for consistency prior analysis using the R-CRAN V3.2.0 software (R Development Core Team, 2011). Statistics aimed to evaluate the propensity for a country to have a significant patient reporting level (>5% for all population) based on the existing information associated with each country.

2.3.1. Outcome and predictor variables selection

Patient reporting percentage was used as the outcome or dependent variable. Patient reporting can be defined as the reports submitted by patients themselves or consumers in general about suspect ADRs to pharmacovigilance authorities, using means of passive or active surveillance. By screening the database for level of response, it was possible to confirm that most countries presented less than 5% of patient reporting, naturally establishing this value as the cut-off for dichotomisation. Accordingly, a binary variable was defined to allow for studying the propensity for each country to report significantly (i.e. >5%) against those with only a residual report (≤5%) (see Table 3 in Results).

From the initial 44 countries, data was complete for 35 countries, considering the identified 42 predictors or covariables, all presented in Table 3. Some of these, as marked in the table, had too many missing values, thus raising numerical problems and were removed from further analysis. Univariate logistic regression models [18] were computed for all considered covariables, as indicated in Table 3. Association with the outcome variable, even if small, was tested through the Wald test, considering at this phase 0.25 as the maximum value for the probability of type I error (i.e. p-value <2.5%). The most significant covariables were selected both from the numerical point of view, as well as from the point of view of interpretation and representativeness. These covariables were then homogeneously grouped by type of information conveyed: health

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Table 1
Sampled countries grouped by continent and marked per patient reporting rate.

Continents and Countries			
Africa	*America*	*Asia & Oceania*	*Europe*
Algeria	Argentina[b]	Australia[b]	Austria[b],
Kenya	Brazil[b]	China	Belgium[b,c], Bulgaria
Morocco[a]	Canada[b,c], Colombia, Cuba	India	Croatia, Cyprus, Czech Republic
Nigeria[a]	Mexico	Israel	Denmark[b,c]
South Africa	Peru	Japan	Estonia[b,c]
	USA[b,c]	New Zealand	Finland[b,c], France
			Germany, Greece
			Hungary
			Ireland, Italy
			Latvia, Lithuania, Luxemburg
			Malta
			Netherlands[b,c], Norway[b,c]
			Poland, Portugal
			Romania, Russia
			Slovakia, Slovenia, Spain, Sweden[b,c], Switzerland
			UK[b,c]

[a] Countries that were removed from statistical analysis due to numerical problems.
[b] Countries included in the statistical analysis.
[c] Countries that showed patients' reporting of >5% of total reports.

Table 2
Countries with adverse drug reaction reporting systems accepting patient reports and its respective percentage of total reports (adapted from Florence Margraff et al. [10]).

Continent and country	Patient reporting rate (% of total reports)	Continent and country	Patient reporting rate (% of total reports)
Africa		Europe	
Morocco	10.4	Austria	5.0
Nigeria	1.3	Belgium	46.0
America		Bulgaria	1.5
Argentina	2.0	Croatia	2.3
Brazil	5.0	Czech Republic	3.5
Canada	30.5	Denmark	34.0
Mexico	1.0	Estonia	9.0
USA	47.6	Finland	13.9
Asia		France	4.0
Japan	3.8	Germany	3.6
Oceania		Hungary	1.3
Australia	3.0	Ireland	2.0
New Zealand	1.4	Latvia	1.0
		Lithuania	0.0
		Malta	0.3
		Netherlands	35.0
		Norway	6.5
		Poland	2.3
		Portugal	1.0
		Slovakia	1.8
		Slovenia	3.0
		Spain	1.6
		Sweden	21.0
		Switzerland	5.0
		UK	13.0

investment (G1), life expectancy and health of the population (G2), and social literacy and organization (G3) (Table 3). Of the initial 35 countries, two were withdrawn from further analysis: Nigeria, which presented values associated with the G2 far from the group average; and Morocco, since reported values were less plausible, even regarding the quality of their pharmacovigilance system.

2.3.2. Statistical analysis for model estimation

Initial non-parametric correlations were calculated to explore possible associations between patient reporting and relevant variables, such as annual growth of pharmaceuticals or total pharmaceutical sales (thus increased population exposure to drugs and possible ADRs) or the year joining the WHO drug monitoring program. Afterwards, and using a multiple logistic regression approach, 3 models were computed using the covariables within each homogenous group, and aimed to identify the most relevant ones within G1, G2 and G3. Once investigated the most significant predictors in each homogenous group, these covariables entered a final model, comprising at least one covariable from each group.

Statistical procedures for both multiple regression stages used a stepwise method and the best AIC (Akaike Information Criterium) as decision criteria for model choice. The final solution was selected based on 3 criteria: discriminatory capacity of the model through the area under the ROC curve, pseudo-R^2, and by comparing the empirical quantiles of the adjusted model with the empirical quantiles of the proportion of significant reports. The pseudo-R^2 using the Nagelkerke (R^2_N) were also calculated, and these are indicators of the amount of information explained by the model [19].

3. Results

In total 35 countries were included in the data analysis. These came from the Americas, Asia and Oceania, and the overwhelming majority from Europe. No country came from Africa. Apart from

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Table 3
Selected covariables, grouped based on the type of information.

Covariables	p-value	Homogenous groups
Adult literacy rate, population 15+ years, both sexes	§	
Average annual growth in public pharmaceuticals expenditure per capita	0.564	
Average of 13 International Health Regulations core capacity scores	0.502	
Adult literacy rate	§	
Antidepressant drugs consumption	0.458	
Antidiabetic drugs consumption	0.526	
Antihypertensive drug consumption	0.777	
Causes of death, communicable diseases	0.348	
Causes of death, non-communicable diseases	0.174*	G2
Full time employees at pharmacovigilance centre	§	
Gross domestic product	0.204*	G1
Gross domestic product per capita	0.005*	G1
Health expenditure, public (% of total health expenditure)	0.03*	G1
Health expenditure, public (% of government health expenditure)	0.462	
Health expenditure, total (% GDP)	0.049*	G1
Healthy life expectancy at birth	0.158*	G2
Hospital bed density	0.081*	G1
Infants receiving three doses of hepatitis B vaccine	§	
Internet users	0.108*	G3
Life expectancy at birth, both sexes	0.555	
Life expectancy at birth, female	0.387	
Life expectancy at birth, male	0.035*	G2
Maternal mortality ratio	0.095*	G2
Mobile phone users	0.893	
Neonatal mortality rate	0.033*	G2
Nursery and midwifery density	0.029*	G1
Out-of-pocket healthcare expenditure (% of private health expenditure)	0.631	
Per capita public health expenditure	0.001*	G1
Per capita total health expenditure	0.096*	G1
Pharmacies per 100 000 population	§	
Pharmaceutical density	0.645	
Pharmaceutical sales	0.025*	G1
Pharmaceutical sales (% of healthcare expenditure)	0.005*	G1
Physician density	0.885	
Proportion of births attended by skilled health personnel	0.725	
Reported number of people requiring interventions against non-transmittable diseases	§	
Skilled health professionals' density	0.017*	G1
Total pharmaceutical sales	0.234*	G1
Total population	0.665	
Under-five mortality rate	0.020*	G2
Urbanized population	0.171*	G3
Year of joining WHO Programme for International Drug Monitoring	0.002	G3

GDP – Gross Domestic Product.
§ Numerical problems.
* Significant covariables (p-value < 0.25).

Argentina, Brazil and Mexico all other were high income countries (Tables 1 and 2). Of these 35 countries entering the data analysis, only 10 of them presented a significant level of direct patient reporting (Table 1). Apart from Canada and the US, the remaining were European countries. Belgium, Estonia, and Finland introduced the possibility of patient reporting in 2012. The other countries have had this possibility for longer, especially Canada and the US, which have it since the 1960s [7]. These countries present a big variability in terms of population, from a small, homogeneous one (e.g. Estonia) to a large and diverse one (e.g. US or UK). Although it was not aimed to provide detailed statistical descriptions of the covariables, the exploratory linear correlation found significant associations according to Table 3.

There are negative correlations between highly consumed drugs and ADRs reporting, but positive with the overall market value. Stronger health systems e.g. having a better professional coverage present also higher patient reporting, this also happening with more Internet usage (Table 4). A negative correlation was obtained with the establishment of the formal pharmacovigilance system reporting to WHO i.e. recent national systems present a poorer patient participation.

Looking to find causal relationships between patient reporting and covariables, univariate regressions were calculated and presented previously (Table 3). After selecting the relevant variables and clustering them, regression calculations within the homogenous groups of covariables selected the following variables:

G1: Per capita public health expenditure and hospital bed density, $R^2_N = 41\%$

G2: Under five mortality rate, $R^2_N = 40\%$

G3: Year of joining WHO Programme for International Drug Monitoring, $R^2_N = 56\%$

Table 4
Selected significant nonparametric correlations between the outcome and covariables used as a potential predictor.

Covariable	Rho
Antidiabetic drugs consumption	−0.423*
Antihypertension dugs consumption	−0.368*
GDP per capita	0.628**
Internet users	0.561**
Life expectancy at birth, both sexes	0.444**
Nursery and midwife density	0.530**
Skilled healthcare professionals density	0.551**
Total pharmaceutical sales	0.447**
Year of joining WHO Programme for International Drug Monitoring	−0.541**

GDP – Gross Domestic Product.
* $p < 0.05$.
** $p < 0.01$.

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Table 5
Covariables in the final statistical model.

Covariable	OR	p-value
Per capita public health expenditure (PPP int. $US)	1.001	0.054
Hospital bed density	0.578	0.087
Under five mortality rate	0.465	0.181

These covariables entered a final model estimation, with a non-relevant predictor abandoning the model (Year of joining WHO Programme for International Drug Monitoring). The final model parameters are presented in Table 5. As explained in the methods section the best AIC criterion was used, justifying one covariable presenting a high p-value, which from a parsimonious theoretical point of view was left in the final solution since countries with low child mortality rate present a good propensity to have a significant patient report.

The model revealed a very good discriminatory capacity with an area under de ROC curve (AUC) of 0.89, allowing to say it is capable of separating countries without significant report from those with more than 5% patient reporting. Additionally, the percentage of explained pseudo-variance equalled 56%, which is a good value regarding the present social and economic areas study field [20].

4. Discussion

The present study aimed to explore characteristics of healthcare systems that could explain and predict an increased patient report of ADRs, or at least could help to separate higher from lower reporting. The initial goal was to move from already identified barriers and facilitators of patients' reporting, many times placed on individuals' features [12,21], i.e. beyond patients' education or motivation. This study wanted to explore associations between organizational and population aspects that should not be neglect if aiming to improve patient reporting and pharmacovigilance effectiveness [9], thus helping authorities to better allocate resources.

It was found a divide between developed countries and developing ones concerning patients' reporting. Low reporting was confirmed for all developing countries, but it was interesting to find countries such as New Zealand, Japan and Germany not following the high-level group. Nevertheless, these countries perform much better in terms of population health status than e.g. the USA. This suggests also that the present study might have limitations on countries data completeness, accuracy and/or detail.

The variables found to be related with an increased patient participation in pharmacovigilance were, by nature, quite ample in scope. The initial correlations showed a high coherency within the database, with expectedly greater reporting for richer and well healthcare-serviced countries, particularly concerning medicines consumption and consequent exposure to drugs side-effects. A higher usage of therapies for non-communicable diseases was associated with less patient reporting, which suggests further investigation on chronic patients' reporting.

General indicators such as public health expenditure and hospital care were significantly predicting a higher patient reporting. These two variables are characteristic of developed countries, which allows speculating that better organized and probably overall efficient systems are already taking pharmacovigilance seriously from the medicines users' end, beyond a professional or expert responsibility. These variables were related to the expenditure on health. Total expenditure on health is defined as the sum of expenditure on activities that, through application of medical, paramedical, and nursing knowledge and technology, has the goal among others, to provide and administer public health programmes [22]. Although this study included a large set of quantitative variables, qualitative ones also play a role. Factors such as the regulatory views on patient reporting, attitude of pharmacovigilance centres, citizen activism, or pharmacovigilance awareness among HCPs and patients can potentially help explain why countries with similar society and economic characteristics [9]. An illustrative example of this is the comparison of Germany and Netherlands, which present very different levels of patient reporting [10]. Pharmacovigilance is at the heart of public health programmes, as it intends to prevent the harm caused by medicines, improve clinical practice, and promote the rational use of drugs [23]. Recently, the world economy suffered an acute recession, causing turmoil in labour, housing, and financial markets [24]. It also impacted health care in a negative way, especially in countries that had to take measures to cut aggressively budget deficits [25]. Recession, followed by austerity measures, are accompanied by a worsening access to health care [26]. In a context of financial crisis or budget cuts, lesser funding of pharmacovigilance activities might lead to a decrease in the patient reporting rate, following the causal relationship found in this study. Although the identified variables that can predict patient ADR reporting are quite ample, future research should not forget the health budgetary matrix, while determining which of the components of health expenditure can make a bigger impact on the reporting levels.

By contrary, several other variables, more specific and theoretically associated with the outcome variable, that could be considered as natural predictors according to linear correlation results, did not prove so. For example, pharmaceutical sales, which can be considered as an indirect indicator of medicines circulating in the market, thus available to most patients and prone to reveal ADR profiles, was not relevant according to study results. Similarly, IT variables such as internet access facilitating communications, as well as the maturity of the pharmacovigilance system, knowing to high level of external relations from long existing centres (e.g. The Netherlands), did not prove to be influential for patient reporting with other simultaneous factors. Physician or pharmacist density also did not prove to be significant to predict patient reporting. Research has shown that one of the motives that lead patients to directly report ADRs is the dismissive attitudes of HCPs [13]. This could explain why a higher density of physicians or pharmacists doesn't impact the propensity of patients to report. Healthcare policies need therefore to be oriented to raise awareness of HCPs to the patient reporting. Pharmacists should be especially targeted, as the scope of their practice is centred in medicines use and converging more into patient-focused clinical services [27].

4.1. Strengths and limitations

To the authors' best knowledge, this is the first attempt to establish a statistical demonstration of causality between sociodemographic and economic factors might be related with a higher propensity to report ADRs by patients. Further research is needed to validate the present findings, especially the concrete items related with health expenditure, and advanced research in this area can concentrate efforts in economic variables instead of losing resources measuring e.g. health professionals' or pharmacovigilance related data.

As referred previously, the present study presents several limitations. One concerns the difficulty to find other potential explanatory variables i.e. more detailed information, such as further economic, social, or pharmacovigilance-specific factors, since for many countries evidence is not complete and/or reports freely available. Even several well-known sources e.g. OECD and World Bank presented an important frequency of missing values. This situation caused numeric issues on model estimation, reducing even further the actual number of variables entering calculations and the chance to build robust models. Furthermore, this study did not evaluate the impact of such factors as regulatory of HCP atti-

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tudes towards patient reporting. These qualitative factors might explain the propensity of countries with similar sociodemographic and economic level to report. Further studies exploring these differences should be planned. It is also important to refer that the data on patient reporting comes from the literature [10]. The year for which the data refers is 2012. Although the authors acknowledge that reporting rates have changes (e.g. in the European Union), we believe the data diversity of the study by Florence Margraff et al. to be an advantage.

Finally, the design of this study was cross-sectional and exploratory. Therefore, it is difficult to make a strong causal inferences, and it might provide differing results if another time-frame is chosen [28]. The results need to be read with due caution.

5. Conclusions

The results of this study shown that health investment-related factors help explain the propensity of patients to report suspected ADRs to the pharmacovigilance system. A healthcare system able to provide secondary care coverage, usually including maternity and infanthood proper care, seems to have also developed strategies to improve population awareness of their contribution to medicines safe use. Notwithstanding, health expenditure is an ample indicator that contains several detailed items. Further research is needed to evaluate which of the health economic and financial items can better explain patient reporting. Running a deeper investigation is advisable to confirm factors that were deemed non-significant but are closely related to pharmacovigilance activities. Qualitative variables were not assessed in this study. These can possibly impact the propensity to report. By further exploring this study results it should be possible provide policy makers with tools to better allocate resources to promote patients' participation.

Conflict of interest statement

Authors have completed the conflict of interest disclosure form and declare no financial relationships with any organizations that might have an interest in the submitted work. There are no other relationships or activities that could appear to have influenced the submitted work. Authors have no support from any organization for the submitted work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.healthpol.2017.10.004.

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