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Original Article

Adverse Drug Reaction Reporting among Healthcare Physicians in Low and Middle-Income Countries: A Cross-Sectional Survey

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Abstract

Because of the paucity of financial, infrastructural, and human resources in low and middle-income countries (LMICs), it is crucial to explore the current knowledge gap and pharmacovigilance practice to adequately deploy resources. To determine the knowledge and practices of ADR among HCPs, we distributed pre-defined questionnaire forms among 1500 HCPs representing 11 LMICs between April 2017 and March 2020. The data was analyzed through Statistical Package of Social Sciences (SPSS) version 22, and frequency and percentages were presented for categorical variables, whereas the comparison of Pakistan and other LMICs was evaluated by performing a $\chi 2$ test. P-value 0.05 was taken as the level of significance between responses. Among 1246 (83%) responses, the majority, 846 (68%), had >3 years of work experience and were males, 805 (64%). Total 788 (63%) responders correctly identified the International Conference for Harmonization-ADR definition, 578 (47%) indicated that all type of reactions should be reported, 167 (14%) believed that anyone can report ADR and only 17 (1.4%) correctly indicated that Drug-Drug Interactions, Medication-errors & Drug-Food Interactions can likely cause ADRs. A total of 562 (45%) participants reported at least one ADR during their practice, and 269 (48%) preferred reporting in their institution. The study findings suggested that HCPs from LMICs have relatively better knowledge about ADR than its reporting. The ADR reporting culture can further be improved through training, awareness programs, and by identifying potential barriers to underreporting.

Keywords: Adverse drug reaction, Healthcare Providers, LMICs, Pharmacovigilance.

Introduction

Adverse Drug Reaction (ADR) is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or modification of physiological function (Schmid *et al.*, 2022)." Most of the marketed drugs, ageing population, and an upward trend in the practice of polypharmacy are contributing factors to the prevalence of ADRs across the globe (Osanlou *et al.*, 2022). The thalidomide tragedy of the early 1960s, resulting in congenital malformations observed in infants of pregnant women administered the drug, prompted the development of drug monitoring systems to cope with drug-related safety issues (Elshafie, Zaghloul, & Roberti, 2018). The international bodies classify pharmacovigilance methods into 4 major categories: passive surveillance or spontaneous reporting, active surveillance, comparative observational studies including stimulated reporting; and recommend submitting ADR reports annually to the WHO Collaborating Centre for International Drug Monitoring in Sweden. The ADR reports act as an important informative tool for Health Care Physicians (HCPs), and the quality of collected ADR reports mostly depends on their reported data (Hussain *et al.*, 2021).

The objective of the study is to determine the knowledge and practices of adverse drug reactions (ADRs) among healthcare professionals (HCPs) in LMICs. Although HCPs know the importance of Pharmacovigilance and ADR reporting, LMICs have scarce resources and awareness, which leads them to neglect the timely reporting of ADRs. This study primarily deals with assessing HCPs in terms of knowledge and practices and then identifying potential gaps to improve the reporting culture in healthcare.

Literature Review

Voluntary or spontaneous ADR reporting, which relies on the active participation of health professionals and consumers, is considered the gold standard for collecting ADR data (Trifiro, Sultana, & Bate, 2018). The most prominent characteristics of spontaneous reporting by HCPs of suspected ADRs are to determine the timely assessment of the risk-benefit ratio of investigational drugs, and it is best to notify of the signals regarding unexpected events and rare ADRs (Adolfo Figueiras, 2023). As per the US 2023 reports, ADR is still the fourth leading cause of death (Yamamoto *et al.*, 2023). Review of reports suggested that 5.3% of hospitalizations are recorded because of an ADR (Zhou and Hultgren, 2020). Over 18 million individual reports have been submitted since the inception in 1968. These reports are stored in Vigibase, the WHO international database of suspected ADRs (Hamid, Rahim, & Teo, 2022).

The World Bank classifies the world economies into four income groups — low, low-middle, upper-middle, and high. Countries with gross national income per capita less than 996 USD are considered low income, those with 996 - 3,895 USD as low-middle income, and 3,896 - 12,055 USD as upper-middle income (Polin *et al.*, 2021). Although several low- and middle-income countries are members of the WHO pharmacovigilance program, pharmacovigilance is still a relatively new concept among health care providers in these regions of the world (Kiguba, Olsson, & Waitt, 2023). ADRs are infrequently reported by the HCPs to the National PV Centers in LMICs, thereby aggravating the problem of under-reporting (Khalili *et al.*, 2021).

To our knowledge, limited studies have been carried out to assess the knowledge and practices of ADR in LMICs. Because of the paucity of financial, infrastructural, and human resources in these countries, it is important to examine the current knowledge gap and PV practice to adequately deploy resources. A better understanding of knowledge and common practices among HCPs in LMICs can guide governments, international funding organizations, and key stakeholders towards the development of effective and viable ADR reporting systems. Therefore, this study aims to determine the knowledge and practices of ADR among HCPs in LMICs

Method

A self-administered questionnaire was distributed to 1500 HCPs in 11 countries (Afghanistan, Cambodia, Kazakhstan, Kenya, Laos, Myanmar, Nigeria, Pakistan, Philippines, Sri Lanka, and Sudan) from April 2017 to March 2020. The participants were approached at various scientific events and academic interactions during the period and were requested to participate in the survey on a voluntary basis.

The study questionnaire was adapted from similar studies, which were briefed to HCPS about the objective of the study and were also provided with a study information sheet. Written informed consent was not required, as there was no risk involved, but a face-to-face interview was conducted after taking verbal consent from each participant.

The participating HCPs were asked seven structured questions administered via face-to-face interaction. The questionnaire comprised three sections, including the demographic characteristics of participants, knowledge of HCPs about ADR reporting, and their practices of ADR reporting. For evaluation of knowledge, participants were provided options for each question, and the correct answer, as cited literature, was considered as true response. Country-wise stratification was done to determine the responses from each country, and a comparison between Pakistan with the rest of the countries (OC) was also evaluated.

Data analysis was performed using Statistical Package of Social Sciences Software, Version 22.0 (IBM, Armonk, NY). Descriptive statistics were applied to the categorical variables and represented as frequencies and percentages. The comparison of knowledge and practices about ADR reporting between HCPs working in Pakistan and other LMICs was also evaluated by performing a $\chi 2$ test. A P-value of 0.05 was taken as the level of significance between responses. This study was commenced after approval from the independent ethics committee by the name of Pakistan Medical Association (Dated: 26th February 2017).

Results and Findings

A total of 1246 survey forms were completed and returned, representing a response rate of 83%. More than two-thirds of the survey participants had 3 or more years of working experience. Most of the respondents, 805 (64%), were males. In total, 779 (62.5%) mentioned their profession type. Of these, 343 (44.1%) were consultants; 36 (10.5%) practice in private clinics, 70 (20.4%) practice in hospitals, and 237 (69.1%) practice in both private clinics and hospitals. The remaining 436 (55.9%) were general physicians; 114 (26.1%) practice in private clinics, 164 (37.6%) in hospitals, and 158 (36.2%) practice in both. Seven hundred and eighty-five (63%) respondents identified the correct definition of ADR as defined by the PV International Conference of Harmonization guidelines. In response to question ‘which of these can likely cause an ADR’, 740 (60%) chose Drug-Drug Interaction (DDI), 394 (32%) Medication Error (ME), 188 (15%) Drug-Food Interaction (DFI); while only 17 respondents (1.4%) selected all these three options. When asked ‘which type of ADR should be reported’, 313 (25%) answered serious ADR, 217 (17%) unexpected ADR, 176 (14%) ADR from new products, 117 (9%) known ADR; while 578 (47%) believed that all types of ADR should be reported. Regarding the question on ‘who can report an ADR, responses were 905 (74%) physicians, 505 (42%) pharmacists, 351 (29%) surgeons, 360 (30%) nurses, and 332 (27%) suggested patients can report an ADR, while 167 (14%) indicated that anyone can report an ADR was presented in Table-1.

Table 1

Knowledge and Practices of HCPs regarding AR reporting in LMICs

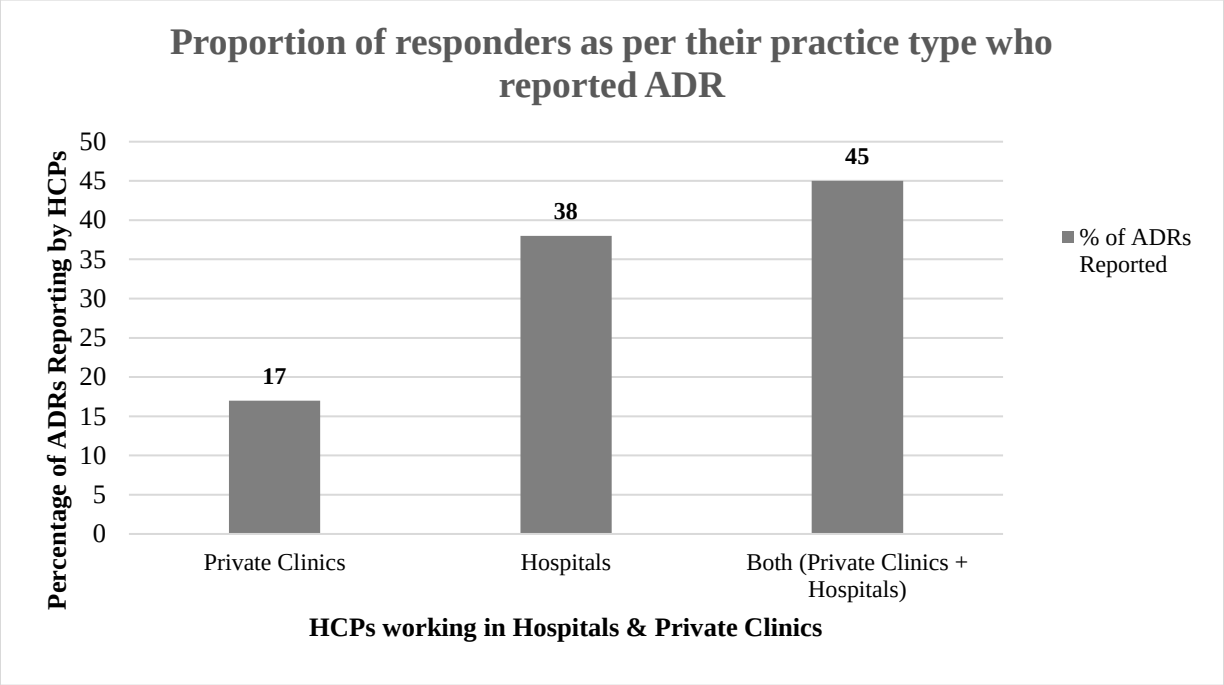
	Overall (n=1246)	Pakistan (n=505)	Afghanistan (n=217)	Philippines (n=143)	Sri Lanka (n=116)	Cambodia (n=110)	Kazakhstan (n=81)	Nigeria (n=42)	Sudan (n=15)	Myanmar (n=7)	LAOS (n=5)	Kenya (n=5)
KNOWLEDGE												
ICH* definition of AR**	63%	72%	36%	85%	71%	48%	32%	81%	47%	100%	40%	80%
DDI***; ME**** & DFI***** : all these can likely cause AR	1.4%	2%	0	1%	4%	0	2%	0	0	0	0	0
Any type of reaction should be reported	47%	51%	26%	68%	54%	25%	49%	52%	53%	29%	40%	80%
Anyone can report AR	14%	8%	5%	18%	30%	21%	9%	45%	13%	29%	20%	60%
PRACTICES												
Reason for Under-Reporting												
Lack of time	22%	16%	20%	13%	36%	17%	51%	43%	20%	29%	20%	40%
Because of the common nature of the reaction	14%	10%	18%	17%	9%	16%	31%	7%	13%	0	40%	40%
Uncertain of how to report	43%	51%	17%	51%	56%	21%	37%	62%	40%	86%	20%	100%
A single report does not make any difference	10%	8%	13%	8%	7%	17%	12%	10%	13%	0	0	40%
Managing the patient was more important than reporting adverse reactions	25%	22%	33%	29%	20%	35%	16%	24%	20%	29%	20%	0
At least once, AR reported	562 (45%)	219 (43%)	118 (54%)	22 (15%)	65 (56%)	57 (52%)	47 (58%)	16 (38%)	12 (80%)	2 (29%)	1 (20%)	3 (60%)
Where to Report												
National Health Ministry	22%	4%	6%	1%	28%	21%	23%	12%	40%	29%	20%	20%
Local Pharmaceuticals	29%	8%	28%	3%	6%	21%	26%	5%	20%	0	0	20%
Multi-National Pharmaceuticals	13%	6%	7%	2%	4%	6%	17%	21%	0	0	0	20%
In own institute	48%	26%	17%	11%	22%	14%	35%	21%	27%	0	0	40%

ICH: International Conference of Harmonization, ** AR: Adverse Reaction, ***DDI: Drug-Drug Interaction, ****ME: Medication Error, ** DFI: Drug-Food Interaction.* ***Data presented in n%.***

The type of HCPs who reported at least one ADR to the relevant authority. Of 543 HCPs, the majority (45%) had both hospital and private clinics shown in Chart 1.

Chart 1

Proportion of responders as per their practice type who reported ADR (n=543)



A significantly higher number of HCPs from Pakistan (PAK) provided a better definition of ADR compared with the pooled respondents from all the other countries (p<0.001). They also showed a significantly better understanding of ADR reporting methods (p=0.009). However, their understanding of how to report ADRs was significantly poorer compared to other countries (p<0.001). When reasons for underreporting were compared, HCPs from Pakistan were more unsure of how to report (p<0.001). Pakistani HCPs did not view lack of time as a constraint for reporting (p<0.001). Compared with other countries, a significantly higher number of HCPs from Pakistan preferred reporting ADR to their institution (p<0.001), were shown in Table 2.

Table 1

Comparison of Knowledge and Practice about AR reporting between Pakistan and other LMICs

	Pakistan (PAK) (n=505)	Other countries (OC) (n=741)	P-value
Knowledge			
ICH definition of AR	72%	56%	<0.001
DDI, ME & DFI can all likely cause AR	2%	1%	0.581
Any type of reaction should be reported	54%	43%	0.009
Anyone can report AR	8%	17%	<0.001
Practices			
Reason for Under-Reporting			
Lack of time	16%	26%	<0.001
Because of the common nature of the reaction	10%	17%	<0.001
Uncertain of how to report	51%	37%	<0.001
A single report doesn't make any difference	8%	11%	0.063

Managing the patient was more important than reporting AR	22%	27%	0.040
At least once, AR reported	219 (43 %)	343 (46%)	0.309
Where to Report			
National Health Ministry	4%	14%	<0.001
Local Pharmaceuticals	8%	17%	<0.001
Multi-National Pharmaceutical	6%	6%	0.954
In own institute	26%	18%	<0.001

Data presented in n (%). The Chi-Squared Test was applied to calculate the P-value among both groups

Discussion and Conclusion

This study found that while HCPs had a good understanding of ADR, they were less likely to report them. The study also showed that HCPs preferred to report ADRs within their institute rather than to the National PV centers.

The results revealed some important findings about the knowledge and practices of HCPs in LMICs towards ADR reporting. Based on the results obtained, the majority (63%) of the respondents were familiar with the definition of ADR, concerning studies published in Northern Cyprus (Turkey), with a reported outcome of knowledge of approximately 80.9 % (Aydin, Aydin and Guney, 2023)While Bhutan had started reporting its ADRs from 2007. One of the cross-sectional studies provided evidence of its poor knowledge of HCPs for ADR reporting; only a few HCPs in our study indicated that anyone could report an ADR. Less than half of the HCPs working in both clinic and hospital settings have reported an ADR at least once in their professional career, which epitomizes the problem of underreporting in developing countries, as previously reported by SAARC countries (Khan, Hamid, & Babar, 2022). Our study, however, established some differences in knowledge of ADR reporting among HCPs.

The comparison with other countries about the definition of ADRs was reported by more than 80 % of respondents from member countries, namely Myanmar, the Philippines, and Nigeria. It is surprising to know that over 65% of HCPs in Kazakhstan were unaware of the definition of ADR despite having several regional ADR centers and being an active member of the WHO International Drug Monitoring Programme, joined in 2008. The WHO has created a comprehensive database named Vigibase, managed and maintained by the Uppsala Monitoring Center (UMC), which has over 35 million reports of Adverse reactions. Guidelines suggest that any HCP or consumer can report adverse events.(Sartori, Aronson, & Onakpoya, 2020).

The study compared the results from other countries with Pakistan and found that pharmacists had better knowledge about ADR reporting. Among HCPs, pharmacists have better knowledge about ADR reporting, knowledge of pharmacovigilance systems, centers, and their estimated value in the range of 80- 90%. It also found that Pakistani HCPs preferred reporting ADRs to the responsible agency within their institution rather than to the national health ministry. This aligns with the bottom-up approach recommended by the WHO, and hospital-based reporting systems can be integrated into a functional national reporting system. Several reasons, including cultural factors and uncertainty about how to report, may account for the preference for institutional reporting (Hussain *et al.*, 2021). Moreover, HCPs from Gondar, Ethiopia, reported that more than 47% had inadequate knowledge of reporting adverse drug reactions. Although they have a positive attitude towards reporting still have inadequate knowledge of practicing timely reporting to their local reporting centers (Seid *et al.*, 2018).

The study identified uncertainty among HCPs about reporting procedures as the foremost barrier to underreporting, which can be improved by providing workshops and training to HCPs (Moinuddin *et al.*, 2018), (O'Callaghan *et al.*, 2018). Moreover, a non-punitive culture for ADR reporting in a healthcare setting is recognized as a confidence booster for HCPs, thereby improving patient safety. Although the response rate of HCPs' knowledge in Saudi Arabia is 70%, only 33% of the respondents know about the National Pharmacovigilance Centers, and 50 %, mostly pharmacists, know how to report ADRs while using the system (AlShammari & Almoslem, 2018).

The strength of this survey is the face-to-face survey technique, which delivers the most representative results and minimizes nonresponse bias (Riordan *et al.*, 2020). Furthermore, the response rate of a face-to-face survey is comparatively higher than other survey methods. In our study, 83% of our sample responded to the survey questionnaire. Nonetheless, time pressure on respondents, geographical limitations, limited data from some countries, and interviewer bias are recognized as possible disadvantages of this study.

HCPs from eleven LMICs have better knowledge of ADRs than ADR reporting, but this could be improved by providing training and lectures. This study showed that many of the HCPs were aware of reporting ADR to the Medication Safety Unit of their institution. This study has also helped in identifying some of the potential barriers to underreporting of ADR in LMICs; uncertainty about reporting procedures was the foremost one. The study findings suggested that HCPs from LMICs have relatively better knowledge about ADR than its reporting. The ADR reporting culture can further be improved through training, awareness programs, and by identifying potential barriers to underreporting.

Limitations

Time pressure on respondents may lead to some information bias in the study. Secondly, based on convenient sampling, the study concluded that limited data from specific populations representing some countries were only part of the survey.

Significance, Contributions, and Recommendations

To identify the knowledge gap among HCPs practicing in different LMICs. Identify the knowledge and practices gap to resolve the potential barrier for future perspective. Teaching and learning perspectives may improve the practices that need to be studied in detail in future studies.

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Data Availability

The data related to this study could be available to the interested audience upon formal request.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Ethical permission

The ethical approval was obtained from the Pakistan Medical Association dated 26th February 2017.

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