

Adverse Drug Reactions Viewpoints, and Reporting Status in Selected Ten Selected Developing Countries: A Brief Commentary

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ABSTRACT

The World Health Organisation defines in 1972 an Adverse Drug Reactions (ADRs) as a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. Edwards and Aronson in 2000 recommend the subsequent definition an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. Very restricted number (500-3000) of people or patient with cautiously, judiciously, and carefully chosen during medicine development stage for testing efficacy and safety of every medicine. There are no pharmacological agents or medicines that are effective to cure or prevent or control any disease is free of adverse effects. The thalidomide tragedy becomes visible in the late 1950s and early 1960s highlighted the inevitability generate the necessity and idea of a national and international program for post-marketing surveillance schemes to monitor the safety of medicines. The countries selected from Asia and conveniently. The articles were selected on basis of browsing in google and google scholar. This review has identified that these developing countries have achieved somewhat improvement but long way to go attain a high standard like of developed countries. Almost all studies reported that diverse educational interventions among varied health care professionals were the sole remedy for reporting ADRs.

Keywords: Adverse Drug Reactions Viewpoints, Developing Countries.

INTRODUCTION

Background and A few Definitions

There has been an ascending surge in the planet human population. Better-quality patient care and better remedies to treat ailments have contributed an essential role in prolonging human lifespan and tumbling morbidity. However, medications also conceivably possess potential to cause hazardous effects to the patients and they are patients often expose ADRs which have been identified as one of the leading cause of hospitalization and may lead to morbidity and mortality¹. The World Health Organisation defines in 1972 an ADRs as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function”². Edwards and Aronson in 2000 recommend the subsequent definition “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product”³. Very restricted number (500-3000) of people or patient with cautiously, judiciously, and carefully chosen during

medicine development stage for testing efficacy and safety of every medicine⁴. Henceforth when any medicine is marketed and prescribed throughout the world for different community and ethnic group several new ADRs detected that was not previously noticed⁴. It is indispensable to monitor ADRs to curtail or avoid impairment to patients stand up from their medicines⁶. Although pharmacovigilance (PV) issue has made major progressions in the developed countries, nonetheless not much has been accomplished in developing countries which still have major ineffective mechanisms and procedures of ADRs reporting and in pursuing PV program and difficulties to monitor properly the injurious effects of medications⁶. ADRs mishap in the developing countries are very grave, unidentified and not revealed, henceforth, divulging an enormous number of people to hazard⁶. Newly developed medicines are entering in the drug market of developing countries at a high speed and in numbers and more rapidly so the burden of adverse events that are resulting from poor quality of management program^{6,7}. It has been claimed that as in developing countries there was a small-scale endeavor was made to assemble, cumulative ADRs and evaluated the reports in public health programs because drug safety did not come in the top priorities of health in developing countries^{6,8}. It

is also true that these countries very often suffer from budget crises. Nevertheless, in a few of developing nations made some exercise to monitor ADRs and PV activities by launching PV centers to safeguard the rational use of medicines^{6,9-13}.

A Brief History

There are no pharmacological agents or medicines that are effective to cure or prevent or control any disease is free of adverse effects¹⁴. The thalidomide tragedy becomes visible in the late 1950s and early 1960s highlighted the inevitability generate the necessity and idea of a national and international program for post-marketing surveillance schemes to monitor the safety of medicines¹⁵. At the time of marketing, limited information about the ADR profile of the respective medicines is available, as the randomized, controlled clinical trials in which new medicines are tested do not reflect the conditions in which medicines are used post-marketing. The basic notion of such programs to attain knowledge about drug safety setback that has not been revealed during medicine development for licensing and marketing, i.e. to recognize indications of new and potentially unidentified ADRs^{16,17}. Patient safeties is an essential basis for any health care throughout the planet. Unfortunately, all health products including medicine have both benefits and risks. Again, at the stage of first marketing, sparse data about the ADR silhouette of the respective medicines is obtainable, as the randomized, controlled clinical trials in which new medicines are tested do not mirror the conditions beneath which medicines are utilized after marketed^{18,19}. Although almost all medicine developed and extensively used in the modern world, their safety profile cannot automatically be generalized to low-income countries, where the incidence, pattern, and severity of ADRs may differ markedly because of local environmental, cultural, and genetic influences²⁰. Most of the developed countries established national PV systems after the thalidomide disaster in the 1960s^{21,22}. Afterward, in 1968, during the 16th World Assembly the 16.36 resolution called for "a systematic collection of information on serious adverse drug reactions during the development and particularly after medicines have been made available for public use"²³.

Reports of A Few Systematic Review and Reasons

One systematic review appraising 37 studies from 12 countries furnishes proof of significant and global under-reporting of ADRs to extemporaneous reporting systems comprising grave or austere ADRs²⁴. Another recent systematic review evaluating 28 research studies reported that much of the information regarding ADRs remains unrevealed and the number and range of ADRs were higher in unpublished than in published versions of the same study²⁵. One more systematic review evaluating 29 research studies to reveal the causes of underreporting found three main causes. Those were ignorance (82.76%), insecurity (82.76%) and indifference (79.31%)²⁶. An additional systematic review analyzing 45 research papers found that medical doctors and trainees (76%) were closely associated with under-reporting. Additionally,

reasons linked with under-reporting were unawareness / inexperience (95%); hesitancy / timidity (72%); exhaustion (77%); indifference and insecurity (67%); and complacency (47%) of studies²⁷. This review also concluded that personal and professional issues had influenced medical professionals much less for under-reporting than was knowledge and attitude²⁷. Similarly, one Spanish study observation that poor knowledge and attitude was the principal factor to influence under-reporting of ADRs²⁸. Age and work experience were noticed also have an influence of under-reporting. Studied respondents mentioned reasons of under-reporting of ADRs were - is not serious, is already known, doubt concerning the causal relationship between the ADRs and the drug, fail to recall for reporting and a lack of time²⁸. The 'seven deadly sins' pronounced by planet most renowned Dr. William Howard Wallace Inman in 1976 as whys and wherefores for under-reporting of ADRs by health professionals. Dr. Inman has amended in 1986 and was re-amended in 1996 to which another sin added²⁹⁻³¹. The causes of under-reporting can largely be classified into two categories by Dr. Inman: i. failure to recognize an ADR ii. failure to report a recognized ADR. Those eight issues are i. Complacency, ii. Fear and Guilt, iii. Diffidence, iv. Indifference, v. Lethargy, vi. Ignorance, vii. The belief that they should be financially reimbursed, viii. Insecurity^{32,33}.

Knowledge, Attitude and Practice of Healthcare Professionals Regarding ADRs - A Few Reports

One Indian study disclosed that mainstream of the health care mavens had good knowledge and attitude about PV and comprehend the necessity for recording and dissemination. This study admits quite a high rate of under-reporting of ADRs even healthcare professionals possess good understanding regarding ADRs. Hence, there was an enormous difference observed between the actual and reported ADRs. The study also detected a positive correlation between an educational intervention and reporting of ADRs. Afterward, educational intervention was much emphasized to promote awareness about ADRs and reporting³⁴. Another study among postgraduate resident doctors revealed that better attitude however low level of knowledge and practices concerning ADRs and reporting. A few study respondents had ever reported an ADR because of the low level of enthusiasm and training in the direction of ADRs reporting. The study also suggests continued medical education to improve ADRs reporting among residents of SSG Hospital and Government Medical College, Vadodara, Gujarat, India³⁵. Another cross-sectional study conducted among medical doctors reported that under-reporting of ADRs is due to poor level of knowledge and attitude towards ADRs³⁶. This study also identified that "inadequate risk perception about newly marketed drugs, fear factor, diffidence, lack of clarity of information on ADR form about reporting, lethargy, insufficient training to identify ADRs, lack of awareness about the existence of PV program"³⁶ as factors influencing under-reporting of ADRs. This study³⁶ also advocated continued medical education to improve ADRs detection and reporting.

Although, healthcare professionals (doctors, nurses, and pharmacists) at the Manipal Teaching Hospital had poor knowledge level towards ADRs and PV nevertheless healthier attitude and practice. Again, most of the study respondents considered ADRs monitoring and reporting, as very important to ensure better healthcare but only a few had ever reported. The principal whys and wherefores for under-reporting were - did not encounter an ADRs or oblivious of the animation of a PV center. Thereafter, the study suggests for continuous education to improve ADRs detection, reporting and sustainability of PV program³⁷. Another Nigerian study conducted among 1439 health professionals [doctors (414), pharmacists (85), and nurses (940)] found that poor level awareness, knowledge gaps and poor attitude towards ADRs detection and reporting³⁸. Another cross-sectional Nigerian study conducted among health-care staffs (doctors, nurses, and pharmacists) of Aminu Kano Teaching Hospital regarding ADRs detection and reporting by means of the yellow card reporting scheme was low. The study also advocated continued medical education to improve ADRs detection and reporting³⁹. Another study conducted among doctors of Father Muller Medical College Hospital, Mangalore, Karnataka, India identified that the level of knowledge and attitude about ADRs detection and reporting were satisfactory on the other hand in real terms of ADRs detection and reporting was poor. Once more, this study also advocates continuous medical education and training of ADRs detection and reporting for all stakeholders of health care⁴⁰.

MATERIALS AND METHODS

The countries selected from Asia and conveniently. The articles were selected on basis of browsing in google and google scholar the keywords: Adverse Drug Reactions, Detection, Reporting, and the country name. The studies incorporated were published 2012-2017. Articles furthermore selected on the basis free download and using Universiti Pertahanan Nasional Malaysia (National Défense University of Malaysia, Kem Sungai Besi, 57000 Kuala Lumpur, Malaysia) link. Thereafter, many efforts have been given to cover as much article can be downloaded free and later utilized to develop the manuscript.

Adverse Drug Reactions Viewpoints and Reporting in Selected Ten Selected Developing Countries Kingdom of Saudi Arabia

One study conducted in Kingdom of Saudi Arabia among health care professionals of Al-Madinah Al-Munawwarah hospitals (Doctors, Nurses, and Pharmacist) reported that most of the study participants wrongly describe the PV term, but they were cognizant of ADRs. Although the majority of them were conscious enough regarding ADRs but their hospital never executed in their hospital. These hospitals were suffering from poor PV system. This study also observed poor level knowledge and awareness exist among the staffs. Thereafter, suggested to set up proper policy planning for educational initiatives to improve knowledge and awareness regarding ADRs and PV for

staffs of this hospital⁴¹. The Incidence rate of ADRs in retrospective and prospective study was 4.50% and 8.2% respectively. ADR was more observed among patients who received multiple medications (5-6), which was higher in prospective (22.1%) than in retrospective (15.5%) study. Again, 0-1 years old patients had maximum ADRs in retrospective (40.7%) and prospective (38.8%) study in. Anti-infective agents were the most frequently observed causing in ADRs in prospective and retrospective study 40.8% and 48.2% respectively. Although none of ADRs were life-threatening. This study concluded that well designed intensive monitoring tactic in PV intensifies the ADRs detection, which can persuade better healthcare especially ensure more drug safety⁴². Another Saudi Arabian study concluded that most of the health care professionals were aware and realize the importance of ADRs and its' reporting. The research participants were confused who and where ADRs reporting should be done. Major constraint observed that poor knowledge level about ADRs reporting procedure and shortage necessary stationeries including forms. Very intensive communication and cooperation between health professionals and organizations have been encouraged for improving ADRs reporting and ensure better health care. Educational intervention has been advocated to improve the total scenario of ADRs and its' reporting⁴³. One more study conducted in Makkah, Saudi Arabia concluded that most of the community pharmacists were ignorant about ADRs reporting system and possesses poor knowledge about ADRs and PV. However, study participants realize the principal reasons for ADRs reporting and described as safe use medicine to ensure better health care for the community. Accordingly, community pharmacists practicing in Kingdom of Saudi Arabia should be provided more education program regarding the concept of ADRs and its' reporting. Thereafter, they can play a positive role for the safe use of medicine in the community⁴⁴. Another similar study also reported that most of the community pharmacists were ignorant of the ADRs reporting. Logistic problems were the foremost obstacles to the ADRs reporting procedure⁴⁵. In conclusion, 32.8% of Saudi patients using methotrexate suffered from at least one ADRs. Most common ADRs reported were gastrointestinal. Interestingly this study ADRs was observed among the younger group of patients with a low number of medications and fewer co-morbidities⁴⁶. This finding was different from earlier study⁴⁷. The incidence of ADRs in retrospective and prospective study was 3.2% and 5.5% respectively. The causality assessment in prospective study reveals that most of the ADRs were probably in 23 (69.7%), followed by possible in 5 (15.1%) and definite in 5 (15.1%). It was detected that patients getting more than 10 medicines in both retrospective and prospective studies developed the highest incidence of ADRs (retrospective study 14.5% and prospective study 15%). The incidence of ADRs was seen uppermost in patients of age more than 60 years in both prospective (55.5%) and retrospective studies (52.6%), and it was found to be statistically significant in

both groups. In prospective and retrospective studies within group analysis, comparing the frequency of ADRs between patients more than 60 years and patients less than 60 years of age ($P < 0.001$ and $P < 0.05$). In both retrospective and prospective studies, the highest incidence of ADRs was induced by antibiotics, in retrospective and prospective study was 36.8% and 48.5% respectively⁴⁸. PV is a new notion in Saudi Arabia. Nevertheless, there is new strategic policy planning adopted by the Saudi Food and Drug Authority and hospitals authority to improve ADRs detection and reporting status⁴⁹.

Republic of India

One Indian study revealed that 8 (14%) patients were admitted due to an ADRs compared to 49 (86%) who were affected by ADRs after hospital admission. Causality assessment through WHO and Naranjo's scale indicated that 42% and 63% respectively of them were possible. The severity of ADRs utilizing Hartwig scale 49% and 12% were reported as moderate and severe respectively. Moreover, 28% (16) and 7% (4) ADRs were and probably preventable respectively of the suspected ADRs based on Modified Shumock and Thornton scale. In 37% (21) and 21% (12) of cases, the ADRs was treated by withdrawal and altering the dose of medicine respectively. While in 25% (14) and 75% (43) of cases the severity of ADRs was safely decreased and patients recovered from the reaction respectively. No fatal cases were reported. 37% (21) dechallenge was done and rechallenge was not conducted among the affected patients. Multiple drug therapy, age, and comorbid diseases were recognized as the foremost predisposing factors for incidence of ADRs. The most important risk factors for producing ADRs were recognized as cardiac problems, smoking, alcohol intake, etc.⁵⁰ Another Indian study reported that 85% (221) study respondents come across up to five ADRs / week. Again, 44.6% (116) opined that up to 10% of the ADRs were serious. The common medicinal groups causing ADRs were antimicrobials (41.6%) and analgesics (15.9%). The commonly observed ADRs were cutaneous (rashes, urticaria, anaphylaxis, and Stevens-Johnson syndrome) and gastrointestinal (nausea, vomiting, gastritis, and diarrhea) 35.7% and 27.7% respectively. The reasons described not reporting ADRs were poor knowledge how (68%) and where (70%) to report the ADRs and poor availability (49.2%) of ADRs reporting logistics⁵¹. Another prospective study was conducted in two medical units of General Medicine, a tertiary care teaching hospital, for about 18 months. The incidence of ADRs was 2.12% (group A, 1.45%, group B, 0.66%). A total of 52% ADRs were serious and 60% of them were preventable. WHO-UMC principles middle-of-the-road of the ADRs in group A were 'possible' (60, $P = 0.008$) in nature while those in group B were 'probable' (28, $P = 0.03$). However, in the Naranjo scale, this difference between groups A and B was much lesser as well as statistically insignificant. The evaluation of the agreement-disagreement among the WHO-UMC principles and the Naranjo scale was 133 or 86%

($k=0.5$)⁵². Another prospective study revealed that incidence rate of antibiotic ADRs was found to be 0.3%. The maximum number of ADRs were reported from the General Medicine (24.48%), tailed by Pediatrics (18.36%), Dermatology (14.28%), Pulmonology (12.24%), Cardiology (10.20%), Nephrology (8.16%), Orthopedics (6.12%), Gastroenterology (4.08%) and Neurology (0.20%). Moreover, this study detected ADRs were Type A (77.55%) and Type B (22.44%) reactions according to Rawlin and Thomson classification. In this study found 57.14%, 20.83% and 23.61% cases the alleged medicine was withdrawn, while no modification, and the dose was modified respectively. The research also found that 55.10%, 38.77%, and 6.12% of the ADRs were preventable, probably preventable and not preventable respectively utilizing modified Shumock and Thornton method of preventability. The causality assessment of the detected ADRs 71.42%, 18.36%, 10.20%, and 0% were probable, possible, definite and unlikely as per the Naranjo scale⁵³. Another Indian study revealed that detected ADRs were 98% and 2% were type B and type A respectively according to Rawlins and Thompson's principles. Again 53%, 45%, and 2% were of mild, moderate and severe in nature respectively⁵⁴. The incidence of alleged ADRs was found to be 2.85%. The patients of 30-59 years experienced (63.2%) maximum ADRs followed by 19.2% and 17.6% of patients of 60 or 60+ years and 10-29 years respectively. ADRs commonly affected were dermatological (24.8%), GI (20%), CNS (19.2%) and respiratory (17.6%)⁵⁵.

The People's Republic of China

China has launched a wide-ranging PV system covering regulation, organization, and technology from 1989 to 2014. As of 2013, one national center, 34 provincial centers and more than 400 municipal centers for ADRs monitoring were included in the four-level (national, provincial, municipal and county) PV system with more than 200,000 remote areas of the country for huddled masses. The China Adverse Drug Reaction Monitoring System is an online spur-of-the-moment reporting system which joins the four-level PV network⁵⁶. One Chinese study revealed that 2.16% of pediatric patients suffer from a serious ADRs and medicine related deaths was 0.34%. This study also found that those patients experienced polypharmacy had a higher rate of serious ADRs than with the single medicine use ($\chi^2=15.99$, $P < 0.0001$). The majority (65%) patient experience ADRs were below 6 years and mainly (<50%) medical doctors were reporting ADRs⁵⁷. Another Chinese study exhibited that 5.11% (71) of ADRs reported cases were serious. Men suffered more in ADRs than women (613/593), and older group (64.03%) patients especially 60 and above suffer more others. The commonest ADRs were itching, rash, dizziness, chills, and palpitations. Skin and related ADRs were highest (55%). The proportional reporting ratio method and Bayesian confidence propagation neural network method were applied for data analysis. The propensity score method to control for confounding factors to detect a headache, dizziness, palpitation, and chills to consider ADRs warning signals⁵⁸. Another study

reported that the number of stated ADRs were 638,996, 692,904, 852,799, 1,200,000 and 1,317,000 from 2009 to 2013, respectively. Healthcare pros furnished significantly higher (80%) portion for reporting ADRs. The Chinese ADRs reporting rates (reports/million inhabitants/year) from 2009 to 2013 were 479, 533, 637, 886 and 983, respectively, which were growing intensely and fulfilled the commendation by WHO. The proportion of new-fangled or grave ADRs reports amplified during the research period from 15.9% in 2010 to 22.1% in 2013 ($\chi^2 = 120.2995$, $p < 0.0001$). The quantity of grave ADRs reports was around 4%. The ADRs reports largely due to antimicrobials and traditional Chinese medicine (TCM), especially TCM injection⁵⁹. In 2015, the national adverse drug reaction monitoring network received 1.398 million ADRs reports, which amplified 5.3% than that in 2014. 393,000 new and serious ADRs cases were reported in 2015, accounting for 28.2% of the total number of the case reports over the same period. ADRs reportage rate grasped 96.6% at the county level; 1044 ADR cases, on mean, were reported per million people⁶⁰. Multifaceted interventions were conducted to improve physician behavior towards spontaneous reporting compliance for ADRs. Interventions were clinician training, education on knowledge, attitudes, and practices, and apposite financial inducements. Thereafter, researchers observed that substantially upgraded ADRs reporting devotion among Chinese medical doctors⁶¹. Afterward, China's ADRs monitoring scheme has attained an advancement in recent years and worked well largely. It was advocates for more research and educational interventions to find the loopholes and blockades in ADRs reporting, enhance risk control actions, and to ensure better health care⁶².

Malaysia

The government of Malaysia has launched the 2nd edition of Malaysian PV Guidelines in 2016⁶³. The 1st edition of Malaysian PV Guidelines was introduced back in 2002. Malaysia also has their own ADRs for checklist and reporting form for suspected ADRs⁶⁴. It has been reported that in equating to other countries, the prevalence of ADRs was more in number in Malaysia. ADRs continued to be an imperative basis of patient impairment and hospitalization. Educational intervention regarding ADRs, monitoring of patients and ADRs, and rational prescribing were advocated for all health care pundits to avoid impending incidences⁶⁵. Nevertheless, in 2016, in a very reputed journal revealed that an overwhelming upsurge in ADRs reporting especially among pediatric patients over the last 14 years' time⁶⁶. The widely held of ADRs reported for children were associated with vaccination and antimicrobials in teenagers. Nurses of public health played the best role in spontaneous reporting ADRs particularly related to vaccination. The occurrence of casualty triggered by reported ADRs in Malaysia is lesser than the touchstone of technologically advanced nations⁶⁶. Another study among pediatric patients below 2 years of age revealed that ADRs were principally connected to antimicrobials. This finding incites to denote the common and high utilization of antimicrobials in children. An immense number of ADRs

in children under 2 years old was primarily persuaded by antibacterials and most were skin related reactions⁶⁷. Under-reporting of ADRs is a major problem in Malaysia. At many occasion this due to inadequate knowledge level. Logistic regression modeling recognized the variable detected ADRs too trivial or too well known to report as the sturdiest prognosticator of not reporting, followed by physicians' category and doubt that the reaction had been certainly instigated by a medicine⁶⁸.

The Democratic Socialist Republic of Sri Lanka

Sri Lankan health care professional such as medical doctors, dentists, pharmacists, and nurses are inspired and motivated to report alleged ADRs come across in their day to day practice. Especially, when a new medicine is first marketed, it would have been verified only in a limited number of patients. Rare ADRs could be recognized only after the medicine is marketed and used by much wider populations. Safety information for use in special clusters such as children, elderly, pregnant women etc. are not often accessible at the time of first marketing of a new drug⁶⁹. A well-established ADRs monitoring and reporting system is essential for any country. As it supports to diminish ADRs associated ailment and overheads to the health care system. It also reinforces the arm of the national regulatory system. Sri Lanka is now a full-time member of the WHO collaboration centre for ADR Monitoring and Reporting, and the Department of Pharmacology, Faculty of Medicine, Kynsey Road, Colombo, is the national collaborating centre. Thus far the number of ADRs information received is far below what is anticipated. The Cosmetic Devices and Drugs Authority should pledge the constitutional and logistical procedures necessary to improve ADRs reporting. Finally, the author concluded that "Sri Lanka is way behind" regarding ADRs reporting, prevention, and management⁷⁰. Another study identified 95 ADRs in all wards of the Teaching hospital Karapitiya over a six-month study period utilizing Hartwig's Severity Assessment Scale. Casualty assessment was conducted utilizing WHO scale detected that 51%, 36%, 9% and 4.5% of patients had moderate, severe, mild, and fatal ADRs respectively. Antimicrobials especially penicillins caused most (27%) of the ADRs but mild and 73% due to other medications. NSAIDs induced ADRs are severe and fatal. Causality assessment detected 44% of ADRs were possibly medicine-related and 30% of them were probably drug related. The average age of patients was 45 years. Skin and the nervous system and gastrointestinal system were commonly affected 31.5%, 26%, and 16% respectively. This research also shows that most ADRs detected were possibly drug related and hence preventable and increases financial encumbrance to the Sri Lankan government⁷¹. One more study reported that among study population 12.6% experienced ADRs, the amount comparable in urban and rural areas ($\chi^2=0.05$; $p=0.82$). Frequently reported ADRs were drowsiness (34.7%), headache (23.1%), gastrointestinal symptoms (18.7%) and dizziness or faintness (11.9%)⁷². Another study reported that out of 715 studied patients 154 ADRs

were detected. 51.9% (80/154) of them were potentially avoidable and 47% (73/154) of ADRs were serious ADRs; 13 were life threatening, 46 caused hospitalization and 14 caused disability. The most common causes for rehospitalization due to ADRs were hypoglycemia due to antidiabetic drugs (17/46), bleeding due to warfarin (6/46) and hypotension due to anti-hypertensives (6/46). ADRs were more common in elderly (34% vs 14.7%, $p < 0.001$), in those who were on ≥ 5 drugs (25.9% vs 12.7%, $p < 0.001$) and among those with diabetes (28.5% vs 15.6%, $p < 0.001$)⁷³. The incidence of ADRs was from head to foot among the research population. A hefty proportion of ADRs were serious. The bulk of ADRs that mandatory re-hospitalization was caused by extensively used medicine and were at least theoretically preventable. The elements linked with a higher occurrence of ADRs were age geriatric patients (≥ 65 years), polypharmacy (≥ 5 drugs) and the presence of diabetes mellitus⁷³.

Republic of Iraq (Al Jumhuriyah al Iraqiyah)

Ministry of Health of Government of Iraq published guidelines for the Iraqi PV System in 2012⁷⁴. The main stream of the research participants' medical doctors (78%) thought that reporting ADRs is part of their responsibility, and monitoring drug safety is similarly imperative (96%). The research results revealed that about 68% of the doctors opined that they did not possess enough clinical knowledge to spot out ADRs. Virtually two-third of the physician's approved that they were not certain that the ADRs are instigated by the medicine. This study also found that the number of the patients treated by doctors per day improves doctors level of knowledge level towards ADRs detection. Continued educational intervention among the different stake holders of health care especially need based course works are considered the best means to motivate and encourage to detect and report ADRs⁷⁵. The majority (62%) of the study participants had perceived ADRs in their professional practice, nevertheless, around 50% of the participants had ever heard about PV. Only 48% were cognizant about the Iraqi PV program. Furthermore, 47.33% of the participants stated that ADRs associated with modern pharmaceutical medicine only should be reported but not the herbal product. The study participants believed that ADRs reporting is a pharmacist's duty and relevant authority of Iraq not working properly 79% and 82% respectively. Interestingly, 60% of research participants revealed that their authority does not encourage to report ADRs. Though 48% and 38% of participants opined that they do not have enough time for reporting ADRs and fearing of facing legal problem respectively⁷⁶. Another the study findings revealed that 64.2% research participants were not cognizant of the Iraqi spontaneous reporting system. The restriction factors which dropping the ADRs reporting among retail pharmacists were identified. These include poor knowledge level ($n=41$; 33.3%), the unavailability of reporting logistics ($n=88$; 71.6%), and ignorance of where to reports ($n=88$; 71.6%) about ADRs⁷⁷. Additionally, 73.3% patients were cognizant regarding ADRs and 37% had personally experienced ADRs in past. Research participants were not

at all had any idea of ADRs reporting center. Moreover, 84.2% and 90% opined that they will report ADRs in upcoming days and strengthen the patient safety respectively. Nevertheless, the majority (61%) research participants pronounced that educational intervention will improve ADRs reporting⁷⁸.

State of Qatar

One study covering all known pharmacist ($n=568$) of Qatar revealed that knowledge regarding of ADRs and reporting understanding was high, but only 29.3% had ever made an alleged ADRs report. The majority research participants stated optimistic attitudes towards PV. A good proportion of participant were lacking behind to diagnose ADRs and access to reporting logistics were professed as obstacles. The study identified hospital pharmacist possesses 7 times high tendency to report suspected ADRs. Most study population were eager to involve in PV work and interested in having more training for prevention of ADRs. Improved educational intervention was advocated to improve efficiency in report submissions to improve better health care⁷⁹. Additionally, another study reported that every public hospital in Qatar enjoys a system for alleged ADRs reporting in which all health care professionals (pharmacists, nurses, and physicians) able to utilize. Most of private the hospitals lack systems to ADRs⁸⁰. A very study revealed that 92 ADRs reports were submitted by different healthcare wage-earners. Most of the physicians' (65.7%), nurses' (62.5%), and pharmacists' (41.0%) reported ADRs were considered of high quality grounded on the WHO quality scheme ($p > 0.05$). A causality assessment using the Naranjo set of rules revealed that 62.2% (possibly) and 31.1% (probably) of the reported ADRs were caused by alleged medications ($p < 0.05$). Furthermore, most of the reported ADRs were type B (54.9%) and unpreventable (64.8%) according to the Medication Appropriateness Index. One hundred percent and 91.2% of nurses' and physicians reported ADRs were for unpreventable, respectively, while 41.0% of pharmacists' reports were for preventable ($p < 0.05$)^{81,82}.

Vietnam

The National Center for Drug Information and ADRs Monitoring established by Ministry of Health (MOH) in accordance with the Decision 991/QĐ-BYT of 24 March 2009 is the leading organization in drug information and ADRs monitoring at the highest level, with its purposes to help the MOH figure up and arrange for drug database together with information on PV, training, doing research, proving guidelines to health institutions at different levels, practicing international cooperation and consultancy, providing services in the field of drug information and PV⁸³. Cephalosporins were recognized as a signal for its adverse effect on cardiovascular disorders, heart & rhythm disorders, and respiratory disorders. The β -lactam group had alike signals like cephalosporin, and aminoglycosides had signal in the nervous system and gastrointestinal disorders. Only one signal was noticed for amphenicols in respiratory diseases. The study showed females were at higher risk of cardiovascular reactions due to cephalosporin and β -lactam than males⁸⁴. The

ADRs reports acquiesced by pharmaceutical houses still acknowledged as a valuable data because of these reports dedicated to reporting principally serious (80.1%), and uncertain (97.5%) events. In addition, this study observed that the rate of ADRs which requires clinical monitoring and laboratory tests were also high. The current study also found that the reporting tendency after the National PV guideline in 2016 appeared much better than before utilizing segmented regression analysis⁸⁵. A strong association between HLA B (*) 1502 and bullous skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis and overlap was confirmed with an odds ratio (OR) of 33.78 (95% confidence interval, 7.55-151.03), $p < 0.0001$, Sensitivity 91.4%, Specificity 76.0%, positive predictive value 84.2%, and negative predictive value 86.4%. The research did not perceive any correlation between the presence of this allele and carbamazepine-induced non-bullous skin reactions (OR 6.33; 95% CI, 0.48-82.74; $p = 0.1592$). The presence of HLA-B (*)1502 in Vietnamese is a pharmacogenetic risk factor for developing carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis⁸⁶.

State of Kuwait

PV has become an international comprehensive struggle that is persistently attaining a speed in the prevention of ADRs. A positive legislative and political determination in Kuwait and in a different place of the region played a significant positive persuasion in planning, establishing, and sustaining an effective PV program⁸⁷. The most of the study participants were knowledgeable about the concepts of PV (61.5%) and ADRs (72.6%) and willing (88.6%) to implement ADRs reporting in their practice. Only 26.8% of participants had previously reported an ADRs and the main reason for underreporting was poor knowledge and skill regarding reporting method (68.9%). Poor collaboration and communication among healthcare professionals and patients (n=62), lack of time and proper management (n=57), lack of awareness of staff and patients (n=48) and no qualified person to report ADRs (n=35) were the principal obstacles for the success of PV program. This study revealed that hospital pharmacists possess good knowledge and positive attitude toward PV and ADRs reporting. However, many them have never reported ADRs. These results suggest that targeted Educational interventions and a well-defined policy for ADRs reporting hopefully promote and increase ADRs reporting and support a PV center in Kuwait⁸⁸.

The People's Republic of Bangladesh

The mainstream of the research respondent (95%) opined that ADRs reporting is a professional obligatory. Poor knowledge regarding reporting, complex reporting system, inaccessibility of reporting logistics, too much workload and lack of time were the main reasons for underreporting. Most of the research respondents recommended regular educational intervention among practicing medical doctors, development of new policy and implementation for implementation at regulatory level, and enclosure of ADRs reporting exercise in the undergraduate and post-graduate curriculum⁸⁹. Another Bangladeshi study among 10,219 tuberculosis patients

was studied among them, 8,047 (78.75%) patients verified no less than one ADRs. Skin-related and hepatic ADRs were 42.95% (4389) 15.99% (1634) respectively. Female patients were more susceptible to ADRs. The incidence of ADRs is mainly ascribed to the combination therapy and long-drawn-out medication for tuberculosis. An immense quantity of ADRs was detected throughout the study period. Henceforth, need close monitoring and managed properly throughout the DOTS therapy to avert lethal ADRs⁹⁰. Overall, 35.5% (72) of the research participants revealed that had experienced an ADRs at their medicine-shop, yet only 51.7% (105) was not accustomed to ADRs reporting system in Bangladesh. The leading four difficulties of ADRs reporting were 'I do not know how to report (Relative Importance Index (RII)=0.998)', 'reporting forms are not available (0.996)', 'I am not motivated to report (0.997)' and 'Unavailability of professional environment to discuss about ADR (RII=0.939)'. Additionally, the most [69.46% (141)] of the research participants were not self-assured the categorization of ADRs (RII=0.889) and were anxious about legal accountabilities and responsibilities related to reporting ADRs (RII=0.806). Furthermore, poor knowledge level about pharmacotherapy and the detection of ADRs was another major factor hindering their reporting (RII=0.731)⁹¹. Another study conducted in the Medicine and Skin outpatient departments of Dhaka Medical College, Dhaka discovered that 19 cases (7 males, 12 females) of ADRs out of 160 patients. 31.58%, 42.1% and 26.32% ADRs were of mild, moderate and severe in nature respectively. In 19 cases, 21 medicines were assumed to cause 25 ADRs. Six patients suffered from multiple ADRs. All the cases of ADR were evaluated for causality assessment by Naranjo's scale and all the 25 ADRs fell in probable category. 56% (14) and 32% (8) out of 25 ADRs exhibited various forms of gastrointestinal and skin related ADRs. Antimicrobials were the mostly blamed medicine. 42.86% (9) and 33.33% (7) were due to antimicrobials and NSAIDs respectively out of 25 ADRs. Fluoroquinolones were identified as the top of the chart⁹².

CONCLUSION

This review has identified that these developing countries have achieved somewhat improvement but long way to go attain a high standard like that of developed countries. Almost all studies reported that diverse educational interventions among varied health care professionals were the sole remedy for reporting ADRs. Incorporation of ADRs detection and reporting in undergraduate medical and other health care studies were also similarly advocated.

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CONFLICT OF INTEREST

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