ASSESSMENT OF KNOWLEDGE, ATTITUDE AND PRACTICES OF HEALTHCARE PROFESSIONALS TOWARDS PHARMACOVIGILANCE ACTIVITES IN LAHORE, PAKISTAN: A MIXED METHODS APPROACH

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DEDICATION

To, the reason for my being!

and

Ammi & Abbu

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
BHU	Basic Health Unit
BSN	Bachelor of Science in Nursing
CARM	Centre for Adverse Drug Reactions Monitoring
CIOMS	Council for the International Organization of Medical Sciences
CME	Continuous Medical Education
CPE	Continuous Pharmacy Education
DRAP	Drug Regulatory Authority of Pakistan
EMA	European Medicines Agency
EU	Europe
FDA	Food and Drug Administration
HCP	Healthcare professionals
HP	Hospital Pharmacist
ICH	International Conference on Harmonization
KAP	Knowledge, Attitude and Practices
KADR	Knowledge about Adverse Drug Reaction
KPV	Knowledge about Pharmacovigilance
LMICs	Low and Middle Income Countries
MBBS	Bachelor of Medicine and Surgery
MNHSRC	Ministry of National Health Services, and Regulation
MOH	Ministry Of Health
NPC	National Pharmacovigilance Centre
N	Nurses
NZ	New Zealand
PDCUP	Provincial drug control unit Punjab

Ph	Physician
Pharm D	Doctor of Pharmacy
PIDM	Program for International Drug Monitoring
PNC	Pakistan Nursing Council
PV	Pharmacovigilance
SADR	Spontaneous Adverse Drug Reaction
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States
USAID	United States Agency for International Development
USP-PQM	United States Pharmacopoeia and Promoting Quality Medicines
UMC	Uppsala Monitoring Center
YCS	Yellow Card Scheme

PENILAIAN PENGETAHUAN, SIKAP DAN AMALAN PROFESIONAL KESIHATAN TERHADAP AKTIVITI FARMAKOVIGILAN DI LAHORE, PAKISTAN: PENDEKATAN KAEDAH GABUNGAN

ABSTRAK

Kesan Advers Ubat (ADR) sering dikaitkan dengan tahap morbiditi dan mortaliti yang tinggi di seluruh dunia. Bagi mengatasi masalah ADR, kebanyakan negara telah menubuhkan sistem pemantauan farmakovigilans (PV) kebangsaan. Kebanyakan sistem PV ini bergantung kepada Laporan Spontan ADR (*Spontaneous ADR Reporting – SADR*) oleh golongan profesional kesihatan seperti pegawai perubatan, pegawai farmasi dan jururawat. Tesis ini meneroka pengetahuan, sikap dan amalan golongan profesional kesihatan terhadap pelaporan ADR, halangan dan juga faktor yang akan meningkatkan aktiviti farmakovigilans di Pakistan dengan menggunakan metodologi bercampur (*mixed methodology*) dan kajian intervensi. Fasa pertama metodologi bercampur dijalankan bagi memahami faktor-faktor yang menyebabkan laporan ADR kurang dilaksanakan di kalangan golongan profesional, dengan menemuramah sejumlah 13 orang pakar perubatan, 10 orang pegawai farmasi, dan 11 orang jururawat. Hasil kajian kualitatif ini mendapati enam tema major iaitu kebiasaan dengan keselamatan ubat-ubatan dan konsep ADR, amalan yang sedia ada berkenaan pelaporan ADR di hospital, kesediaan untuk menerima perubahan amalan, latihan yang diperlukan untuk memperbaiki amalan melaporkan ADR, halangan terhadap pelaporan ADR, pengiktirafan dan pengenalan diri sebagai penjaga keselamatan ubat-ubatan dan keperluan perubahan di dalam sistem yang sedia ada. Untuk mendapatkan pemahaman yang lebih mendalam tentang hasil kajian kualitatif tersebut, fasa kedua metodologi bercampur telah dilaksanakan melalui satu soal selidik

kajian keratan rentas yang melibatkan golongan profesional kesihatan (n = 346) dari hospital awam tertiari. Dengan jumlah maklumbalas sebanyak 89.87%, kajian ini menunjukan bahawa kebanyakan pegawai farmasi mempunyai pengetahuan yang lebih baik terhadap laporan ADR (89.18%) dan farmakovigilan (81.08%) berbanding dengan pakar perubatan dan jururawat. Tambahan lagi, kebanyakan pakar perubatan (67.0%) dan jururawat (77.2%) hanya membuat laporan ADR secara lisan sahaja, berbanding dengan pegawai farmasi (91.9%) yang melaporkan ADR melalui borang ADR. Halangan yang dikenalpasti oleh ketiga-tiga golongan profesional kesihatan ini termasuk; kesuntukan masa untuk membuat laporan oleh 42.0% pakar perubatan (n=47), 37.8% pegawai farmasi (n=14) dan 39.6% jururawat (n=78); tidak sedar bahawa ADR telah berlaku oleh 47.3% pakar perubatan (n=53), 37.8% pegawai farmasi (n=14) dan 36.5% jururawat (n=78) dan tidak tahu akan sistem pelaporan ADR dan sistem PV tempatan oleh 36.6% pakar perubatan (n=41), 27.0% pegawai farmasi (n=10) dan 34.5% jururawat (n=68). Fasa kajian (kuantitatif) ini telah mengenal pasti jurang dalam pengetahuan mengenai laporan ADR di kalangan golongan profesional kesihatan dan ini mengesahkan penemuan kajian kualitatif. Berdasarkan penemuan ini dan untuk mengkaji sama ada intervensi pendidikan akan dapat membantu meningkatkan status pengetahuan golongan profesional kesihatan mengenai pelaporan ADR, satu kajian intervensi pendidikan berbentuk bengkel sehari telah direka dan dijalankan. Bengkel pendidikan tersebut melibatkan 61 pakar perubatan dan dijalankan dalam jangka masa 1 hari. Penilailan pengetahuan pra dan pos bengkel intervensi dilakukan untuk mengukur impak program pendidikan ke atas tahap pengetahuan peserta. Tiada perbezaan yang signifikan dalam penilaian pengetahuan pra-pos pelaporan ADR ($p<0.919$); walaubagaimanapun, perbezaan yang signifikan didapati dalam penilaian pra-pos mengenai pengetahuan peserta mengenai sistem

farmakovigilan ($p < 0.001$), di mana terdapat peningkatan dalam tahap pengetahuan peserta. Kesimpulannya, tesis ini mengesahkan bahawa wujudnya jurang pengetahuan dalam laporan ADR di kalangan golongan profesional kesihatan di Pakistan. Faktor yang dikenalpasti menyumbang kepada kadar laporan yang rendah dan ini menekankan kepentingan untuk mewujudkan strategi yang sesuai untuk meningkatkan dan memastikan kelestarian pelaporan ADR.

ASSESSMENT OF KNOWLEDGE, ATTITUDE AND PRACTICES OF HEALTHCARE PROFESSIONALS TOWARDS PHARMACOVIGILANCE ACTIVITES IN LAHORE, PAKISTAN: A MIXED METHODS APPROACH

ABSTRACT

Adverse Drug Reactions (ADRs) are associated with a high rate of morbidity and mortality worldwide. To overcome the ADR related problems, many countries around the world have established national pharmacovigilance (PV) systems. Most of the PV systems rely on Spontaneous ADR reporting (SADR) by healthcare professionals (HCPs) such as physicians, pharmacists, and nurses. This thesis aims to explore the knowledge, attitude and practices of HCPs, by using mixed methodology and an intervention study regarding ADR reporting in Pakistan and perceived barriers and facilitators to improve pharmacovigilance activities. The first phase of the mixed methods study was conducted to understand the reasons behind the ADR underreporting among HCPs, by conducting an interview with a total of 13 physicians, 10 pharmacists, and 11 nurses. The finding from qualitative study revealed six major themes as familiarity with medication safety and the ADR concept, current system of practice and reporting of ADR in hospital setting, willingness to accept the practice change, training needed to improve ADR reporting, barriers related to ADRs reporting, recognition of the role as custodian of medicine safety and system change needs. To get a deeper understanding of the findings from the qualitative study, second phase of mixed methods, i.e., a cross-sectional questionnaire-based survey was employed by involving HCPs (n=346) practicing in tertiary care public hospitals. With a total response rate of 89.87%, %, the survey findings revealed that most of the pharmacists showed better knowledge towards ADR reporting (89.18%) and pharmacovigilance

(81.08%) as compared to the physicians and nurses. Besides, many physicians (67.0%) and nurses (77.2%) reported the ADRs verbally, while majority of the pharmacists (91.9%) reported an ADR on ADR forms. The most common barrier identified by all three healthcare professionals included, lack of time to report an ADR by 42.0% physicians: (n=47), 37.8% pharmacists (n=14) and 39.6% nurses (n=78), lack of knowledge if an ADR happened by 47.3% physicians (n=53), 37.8% pharmacists (n=14) and 36.5% nurses (n=78), about 36.6% physicians (n=41), 27.0% pharmacists (n=10) and 34.5% nurses (n=68) had no information about ADR reporting system and local PV system based policies. This (quantitative) phase of the study identified gaps in the knowledge regarding ADRs reporting among HCPs and this confirmed the findings of the qualitative study. Based on these findings, and to explore whether an educational intervention will improve the current knowledge status on ADRs reporting, an educational intervention study was designed and conducted. The intervention study involved 61 physicians, who attended a one-day based workshop, and a pre and post evaluation of knowledge was performed. There were no significant differences in the pre-post evaluation of knowledge about ADR reporting ($p<0.919$); however, a significant difference was found in the pre-post evaluation of participant's knowledge regarding pharmacovigilance system ($p<0.001$), thus showing an improvement in the knowledge of participants. In conclusion, this thesis confirmed the existence of a knowledge gap in ADR reporting among Pakistani HCPs. The identified factors contributing to the low level of reporting emphasized the need to determine appropriate strategies to enhance and sustain ADRs reporting.

CHAPTER 1

INTRODUCTION

1.1 Background

A drug may cause three possible reactions, one, that is wanted, two, that is unwanted and three, that we do not know about (Hema and Bhuvana, 2012). An adverse drug reaction (ADR) is the one that has an unknown etiology, causing an enormous fiscal burden on both the society and the healthcare system. Medicines during clinical trials are evaluated only for their safety profile on carefully selected individuals and there is a possibility of an ADR, that remained unexplored during the clinical trials due to the exclusion of special populations, such as elderly, children, pregnant females and others. ADR happens due to the number of reasons, such as the clinical trial data is limited to a specific population, patients may experience co-morbidities, off-label use of drugs or variation in the genetic makeup of individuals (Moore and Bégaud, 2010).

There is always a tradeoff between medicines' side effects and therapeutic benefits. However, evidence suggests that ADRs are very common, and may lead to hospitalization and even death (World Health Organization, 2014). The Thalidomide disaster, which took place half a century ago, is still perceived as a big tragedy in the history of healthcare. It caused more than 100,00 children to be born with birth anomalies to pregnant mothers, who had used the drug to treat morning sickness problems (Nkeng et al., 2012). The incident marked the failure of medicine regulation, weak approval process, delayed recognition of causes of adverse effects, hesitant

approach by regulatory bodies to take the action and the lack of communication with the patients and the healthcare professionals (HCPs) (Caduff-Janosa, 2017).

To address these issues, World Health Organization (WHO), established a program for monitoring of drug safety as a pilot project in 1968, initially ten countries joined this project and as of June 2019, now 166 countries are the members of the WHO Program for International Drug Monitoring (PIDM). Moreover, 136 countries are submitting ADR reports to the VigiBase; a WHO global database of ADRs (World Health Organization, 2019a; World Health Organization, 2019b). In 1971, WHO established its first pharmacovigilance center in Uppsala, Sweden, known as Uppsala Monitoring Centre (UMC) (World Health Organization, 2015). Now UMC has pharmacovigilance collaborating centers all around the world.

Pharmacovigilance (PV) is defined as "the science and the activities concerning the assessment, detection, understanding and the prevention of the harmful results or any adverse drug-related issues" (Uppsala Monitoring Centre, 2018a). Many developed countries have successfully established strong pharmacovigilance systems in their countries. The system is meant to report suspected ADRs that are encountered by HCPs in their clinical practice. PV center collects spontaneous reports on possible drug related issues to detect the ADRs in the post-marketing phase (Rolfes et al., 2014). This spontaneous reporting is considered as the most important feature of the PV system whereby the reports are submitted to the national reporting agency through HCPs, general public and pharmaceutical manufacturers. These reports are then communicated to the WHO pharmacovigilance center (Uppsala Monitoring Centre, 2018b). Suspected ADRs reports from member countries of the WHO Program for International Drug Monitoring are sent to the WHO international database 'VigiBase',

which is managed by the WHO Uppsala Monitoring Centre (UMC). The reports are then reviewed, analyzed and the evidence-based recommendations are forwarded to the member countries (Uppsala Monitoring Centre, 2017). Thus, Thalidomide tragedy served as a wakeup call that led to the strengthening and significant improvement of drug regulatory and monitoring systems worldwide (Caduff-Janosa, 2017).

1.2 Mechanism of Adverse Drug Reaction Detection

To save the patients from perceived harm of medicines and to improve public health, the development of a mechanism is crucial. This mechanism can help, evaluate and monitor the medicine safety in clinical use. The system in practice is known as Pharmacovigilance (PV), which is an umbrella term and comprises of effective drug regulation systems, public health programm and clinical practice to describe the process for ADR monitoring and its evaluation (World Health Organization, 2014).

A comprehensive and an efficient PV system not only considers identification of risks in data collection but also takes into account risk evaluation, its minimization and communication of risks, thus saving the population from harmful effects of drugs. This is done through a structured manner by taking appropriate decisions to improve safe use of medicines (USAID, 2009).

Post marketing pharmacovigilance activities such as spontaneous reporting of adverse drug reactions, cohort event monitoring and study of archived data provide more relevant data with larger sample size and longer follow up period. This is necessary for accurate and ongoing evaluation of the risk benefit ratio of healthcare interventions (Black, 1996; Yang et al., 2010). Pharmacovigilance methods can be selected based on the situation, such as product, the population, the indication and the

problems to be addressed. The selection of method also depends upon the outcome, such as need to identify the risk or missing information or to detect a signal or to demonstrate the medicines safety (European Medicines Agency, 2005).

There are several pharmacovigilance methods listed below:

1.2.1 Passive Surveillance

The most common method used in pharmacovigilance is the passive surveillance which relies heavily on the spontaneous reporting of any suspected ADR experienced by the patients. The drawback of passive surveillance is that it may not generates large volumes of data, or accurate, complete or product specific report of an ADR, such as in the case of spontaneous reporting of an ADR. Thus, limiting the scope of comparisons related to the target and subject specific surveillance. However, passive surveillance may generate signals, which can be further taken up by active surveillance for further inquiry (USAID, 2017).

1.2.2 Stimulated Reporting

The reporting of adverse events to facilitate reporting by HCPs, when a new product is introduced for a limited time exposure (Strom, 2000). Such reporting includes online reporting and systematic evaluation of drug related incidents based on a pre-designed method. Pharmaceutical manufacturers, during post marketing, may also provide safety information of drugs and may encourage HCPs to report any untoward effect towards the use of medicines. Stimulated reporting does not provide data to accurately generate incidence rates but can help in the estimation of reporting rates (European Medicines Agency, 2005).

1.2.3 Active Surveillance

Active surveillance seeks to collect the complete information about adverse events via a preorganized and continuous process. It can be done through a risk management program, where a patient is followed up for a specific drug and may be asked to fill a survey form for future contact. The process of collecting ADRs reports through active surveillance is better than passive surveillance as comprehensive data can be collected in this process (European Medicines Agency, 2005).

1.2.4 Post Marketing Surveillance and Spontaneous Reporting

Post marketing surveillance is concerned with the techniques for the detection and measurement of incidence of ADRs (Inman, 1986). It refers to the analysis of data collected for the purpose of detecting adverse effects after a drug receives marketing approval (Praus et al., 1993). It deals with the signal detection and evaluation as a result of spontaneous reporting of an ADR. It was first introduced in 1960s in response to the delayed recognition of the association between Thalidomide use in pregnant females and congenital limb deformity (Stephens and Brynner, 2009).

Spontaneous reporting is a type of passive surveillance referred to as an unsolicited communication by a patient, a healthcare professional, or a consumer to a company, regulatory body or to the other organization (e.g., WHO, regional or national pharmacovigilance centers or poison control centers). In the report they describe adverse drug reaction experienced by a patient, who was administered with one or more medicines and that provides a real-life experience of a medicine use (European Medicines Agency, 2003). It can report both known and unknown or undocumented adverse events whether serious in nature or not. Drug related adverse events can be

due to problems related to drug quality (or medical devices), drug interactions, medication errors (USAID, 2017).

The process of spontaneous ADR (SADR) reporting is inexpensive, simple, as reports are voluntarily submitted by HCPs, consumers and patients. The data obtained from these reports are entered into a database to detect any signal. Sometimes, the reporters for spontaneous ADR reporting can be contacted for follow-up of a report based on its importance and the extent of information collected (Waller, 2006). Once a signal is identified, then all relevant available information from other sources is analyzed (Waller and Lee, 1999). As signal evaluation requires resources and due to generation of large number of signals from the database, the involvement of triage and impact analysis becomes a priority (Ståhl et al., 2004, Waller et al., 2005, Heeley et al., 2005). To complete the process of reporting, information must be conveyed to reporters through acknowledgement and through a bulletin describing the signals (Waller, 2006). Since late 1980s, International Conference on Harmonization (ICH) and the Council for the International Organization of Medical Sciences (CIOMS) have established International standards of reporting related to what, when, why and how an ADR should be reported (Bahri and Tsintis, 2005).

Spontaneous reporting has a major contribution in the detection of safety signals in the post marketing surveillance. It may help in the identification of rare adverse events, which remain unrecognized during clinical trials. It also provides help in the recognition of data which could be helpful for risk factors and clinical manifestations of known serious ADRs of the medicines. However, attention should be paid, once data regarding spontaneous report of ADR is evaluated, especially when comparing several drugs. The contributing factors may vary from the indication of

drug use, time of reporting about a drug since its launch in the market, activities of concerned drug regulatory authority and attention of media (Faich, 1996; Goldman, 1998; Pinkston and Swain, 1998; Hartmann et al., 1999).

1.3 Organization of Pharmacovigilance Activities

Pharmacovigilance activities in any country are carried out by the help of regional or local centers in these countries that collect ADR reports (serving as alarm signals), design surveys and other pharmacovigilance studies, and provide additional information on drugs. Concerns about possible ADRs and requests for information about a drug is directed to the appropriate regional pharmacovigilance center. In recent years, regional centers have expanded their pharmacoepidemiology activities such as finding associations between specific ADRs and factors such as age, gender, dosage, population phenotype, concomitant use of other medicines as well as environmental factors. The information is further communicated to the national pharmacovigilance center, which considers specific measures such as drug withdrawal from the market, modification in drug classification and restricting the approved uses of a drug, evaluation of risk-benefit ratio of drug, sending additional information to physicians and submitting the ADR reports to the UMC (Montastruc et al., 2006).

Apart from all the above-discussed pharmacovigilance activities, the main role of the pharmacovigilance system is associated with signal detection, a core activity of UMC, which aims to find and describe medicines associated with suspected harm to patients. Signal detection happens through the evidence provided by healthcare professionals in the form of spontaneous reporting of ADRs, or reports submitted by pharmaceutical companies and patients. A signal is considered as a hypothesis of a risk associated with a medicine supported by arguments and data (Uppsala Monitoring

Centre, 2019). Globally, most of the pharmacovigilance systems depend upon the information about ADRs, which is communicated through the spontaneous reporting systems, the reported information from HCPs is entered into the database and is regularly assessed for the signal generation (Edwards and Biriell, 1994; Waller and Harrison-Woolrych, 2010). During the post-marketing phase of an approved drug, spontaneous adverse drug reaction reporting (SADR) is used for the risk-benefits evaluation and monitoring of new drugs (Lexchin, 2006). However, the SADR reporting is greatly affected due to the under-reporting of ADRs by HCPs. The reasons could be many, however, due to many challenges, the causes for under-reporting are not documented well in developing countries. However, the literature suggests that these are outlined in the studies from developed countries (Inman, 1976; Bateman et al., 1992; Belton et al., 1995; Vallano et al., 2005).

Since the last decade, there had been an increase in the number of studies published in developing countries regarding knowledge, attitude, and practices (KAP) of HCPs regarding pharmacovigilance (Thomas and Zachariah, 2018). Knowledge depicts understanding, attitude reflects the emotional, motivational, cognitive and perceptive beliefs that have a positive or negative influence on an individual's behavior or his practice. The action of healthcare professionals about the observation, assessment, reporting or taking other actions is perceived as practice (Thomas and Zachariah, 2018). Knowledge and attitudes can influence practice, as knowledge builds up a certain attitude, which can lead to an improvement in practice. Similarly, practical experiences may help to groom the knowledge and attitude over time (Abubakar et al., 2015). In developing countries, the gap from knowledge and attitude to practice is high regarding pharmacovigilance activities among HCPs, thus it requires improvement (Kamtane and Jayawardhani, 2012; Thomas and Zachariah, 2018).

The Pakistani pharmacovigilance system like other spontaneous adverse drug reaction reporting SADRs around the globe suffers from under-reporting of ADRs from healthcare professionals. At the time of undertaking this work, little information was known about Pakistani HCPs' knowledge, attitude and practices (KAP) towards ADR reporting.

1.4 Justification and Rationale of the Study

Like any other country, the need for safe and appropriate use of medicines and the challenges to ensure medicines safety remains crucial. Pakistan is in a dire need to overcome the challenges faced by the healthcare system and healthcare professionals have an important role to play to overcome these challenges. Globally, patient safety stands as a major concern for all healthcare providers, thus requiring them to act more vigilant during their routine practices.

Data generalizability remains very challenging from developed countries to the developing world where the major difference lies in the healthcare system, living style of population and resources available to the population and HCPs. At present, the data about pharmacovigilance activities in Pakistan is scant and below par. There is a lack of awareness and involvement of HCPs, including physicians, nurses, and pharmacists in recently introduced medicines safety programs and pharmacovigilance activities. In this context, it presents the HCPs with the immense challenge to cope up with the recent and future trends in medicine safety.

In order to develop strategies to improve the medicine safety practices in Pakistan, it is necessary to explore the awareness and practice domains related to HCPs to improve the PV system in particular and the health system in general.

Lahore, being the provincial capital of Punjab, Pakistan is the most populous city and that is why it is being selected to undertake the current study. Besides, provincial government head offices are in Lahore. The city has the highest number of tertiary care public hospitals within the province and is considered as the most facilitated and developed city of the Punjab province. Hence the study aimed to gain an insight into the knowledge, attitude and practices of healthcare professionals to explore the causes of under-reporting of ADRs.

1.5 Research Questions

The present study was designed based on the following questions:

1. What is the level of knowledge, awareness and attitudes of HCPs in Lahore regarding PV and PV based activities?

2. What are the current patterns of practices of ADR reporting in the public hospitals of Lahore?

3. How well-prepared healthcare professionals are to undertake the role in medication safety provision?

4. What barriers HCPs face while undertaking ADR reporting?

5. What could be the facilitating factors that can improve the reporting of ADRs among HCPs?

1.6 Significance of the Study

The current study will be able to be utilized by government and policymakers to formulate policies and action plans for the betterment of safe use of medicines and the ADR reporting system in the country. It is expected to serve as a guidance to improve the medicine use practices by the healthcare professionals and hence will provide a road map to the safe use of medicines in country.

1.7 Objectives of the study

The study was conducted with the following objectives:

1. To explore the knowledge and attitude of HCPs towards the pharmacovigilance system
2. To document the current practices of healthcare professionals regarding ADR reporting
3. To determine the knowledge and competency needs about pharmacovigilance and its activities
4. To explore potential barriers and provide key solutions regarding forming viable pharmacovigilance system in Lahore.
5. To evaluate the impact of educational intervention on the knowledge of physicians towards ADR reporting and pharmacovigilance.

1.8 Overview of the Thesis

The present study employed a mixed-methods approach that involved both qualitative and quantitative methods. This mixed-methods study on this topic was conducted for the first time in Pakistan. It explored the knowledge, attitude, and practices of HCPs in the Lahore, Pakistan.

The study is divided into two rounds: first round consolidated the qualitative and quantitative phase. While the second round of the study is comprised of an intervention phase.

This thesis is comprised of 9 chapters, including this chapter, and each chapter stands as an individual chapter.

Chapter 1 is the introductory chapter and provides a general overview of the research problem statement. It presents the general flow of the current research and organization of the thesis.

Chapter 2 describes the literature review, starting with the overview of pharmacovigilance, adverse drug reaction and its impact on the public healthcare system. It also discusses the different systems of pharmacovigilance worldwide, followed by the pharmacovigilance system in Pakistan.

Chapter 3 discusses the general methodology which is adopted to design and conduct the present study. It comprises of the mixed methods design with an emphasis on quantitative and qualitative studies. It explains the basic concepts of these methods and outlines how the mixed methods approach is a better choice to achieve the study objectives.

Chapter 4,5 and 6 includes the qualitative study based on the exploration of knowledge, attitudes, and practices of physicians, pharmacists, and nurses working in tertiary care settings in Lahore, Pakistan. The chapters also include a detailed discussion on the barriers faced by these HCPs during performing the pharmacovigilance activities.

Chapter 7 includes the quantitative study conducted among HCPs from tertiary care public settings in Lahore, Pakistan. It is a questionnaire-based survey and it summarizes the current practices of pharmacovigilance and missing elements regarding pharmacovigilance in the healthcare system of Pakistan.

Chapter 8 includes the pilot intervention study, which included physicians' assessment of knowledge before and after the educational intervention. It is a questionnaire-based study, and it shows the impact of education as a way forward to the improvement strategy for the promotion of pharmacovigilance activities.

Chapter 9 concludes the findings from the mixed methods-based design; besides, it also provides several suggestions on the improvement of the pharmacovigilance system in Lahore, Pakistan.

CHAPTER 2

LITERATURE REVIEW

2.1 Background

Modern medicines have changed the way of management and control of disease, however despite having beneficial effects, they cause adverse drug reactions (ADRs) contributing towards disability, morbidity, and mortality (World Health Organization, 2014). In this context, the safe use of medicines is vital as it affects each member of the society (Edwards and Aronson, 2000). Despite medicines' utility in the treatment and prevention of disease, it sometimes may result into undesirable or even fatal reactions and even in some countries, ADRs are listed among the top ten causes of mortality (White et al., 1999).

An ADR is defined by WHO "as a response to a drug that is noxious and un-intended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (World Health Organization, 2002). The risk of ADR is associated with the drug use including dose, administration frequency, pharmacodynamics and pharmacokinetic characteristics of population comprising of pediatric, geriatric patients or those with the hepatic and renal impairment (Sultana et al., 2013). Such conditions require special attention in regard to ADR monitoring, thus ADRs contributing towards additional economic burden on patients, caregivers and healthcare systems.

2.2 Hospital Admissions and Adverse Drug Reactions

Since early 80s, many studies reported that ADRs were the causes of hospital admissions with reporting rate of 2.9 to 6.0 percent. The hospital admissions due to ADRs incidents were found in the range of 1.5 to 20% and were higher than that to the total admissions to hospitals (Black and Somers, 1984; Lazarou et al., 1998; Baker et al., 2004). A study by Classen et al. (1997) reported that during 1990-1993, the ADR incidence related hospital admissions were 2.43 per 100 admissions (Classen et al., 1997). Similarly, Bates et al. (1995) found ADR related admissions as 6.5 ADRs out of 100 admissions (Bates et al., 1995). Pirmohamed et al. (2004) conducted prospective analysis of 18820 admissions in UK based hospitals accounting to the 1225 ADR related admissions and found that there was a high burden of ADRs in terms of morbidity, mortality and cost to National Health Service (NHS) (Pirmohamed et al., 2004).

Wu et al. (2010) analyzed a ten years trend of hospital admissions related to ADR in England and found that 557,978 admissions were related to ADR, presenting 0.9% of total patient admissions due to ADR. During this period, the number of ADRs incidents increased from 42,453 to 75,076 and mortality rate increased from 4.3% to 4.7% (Wu et al., 2010). A prospective study conducted in public hospitals of France in 2006-2007 showed that out of 2692 admissions, about 97 admissions were related to an ADR, whereas one third of the ADRs were found to be preventable (Bénard-Laribière et al., 2015). Schneeweiss et al. (2002) between 1997-2000 conducted a longitudinal population-based study and found that among 10,000 hospital admissions, 9.4 admissions were drug related in Germany (Schneeweiss et al., 2002). Contrary to

this, the data regarding ADR related hospital admissions is scarce in developing countries (Ramesh et al., 2003).

2.3 Spontaneous ADR reporting: A core component of pharmacovigilance

'Spontaneous reporting of an adverse drug reaction can be defined as, "an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional Centre, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme" (International Conference on Harmonization, 2003).

During the post-marketing phase of an approved drug, spontaneous ADR reporting is considered a cornerstone for benefit-risk evaluation and monitoring of drugs (Lexchin, 2006). Spontaneous ADR (SADR) reporting is also considered fundamental for drug safety surveillance (Desai et al., 2011). Out of several ways of detecting ADRs, SADR methods of reporting has played an important role to improve the Pharmacovigilance (PV) system in many countries (Vallano et al., 2005; Waller, 2006). The method of reporting has been employed by many national pharmacovigilance centers around the globe as a useful tool to timely detect and minimize drug-related morbidity and mortality (Pal et al., 2013). Although the system is easy to operate, inexpensive and covers all drugs and patient populations, however due to under-reporting and inability to calculate the incident rate of ADRs, it is estimated that only 6-10% ADRs are reported (Herdeiro et al., 2005). Hence under-reporting of ADRs has a prominent impact on the benefit-risk ratio for medicine safety

evaluations especially when spontaneous reporting is the only or main source for reporting (Clarke et al., 2006).

The field of pharmacovigilance deals with the reports that raise concerns over the post-marketing safety of the drugs that often result in an adverse drug reaction. Many developed countries have successfully established strong pharmacovigilance systems (Yadav, 2008). These systems are meant to report suspected ADRs that are encountered by healthcare professionals in their clinical practice (Moride et al., 1997; Oshikoya and Awobusuyi, 2009).

2.4 The global system of Pharmacovigilance

In the UK, according to Yellow Card scheme, every year almost 17,000 ADR reports are reported and hospital pharmacists in UK are officially responsible to report ADRs (Rabbur and Emmerton, 2005). In the US, several major national programs are working to ptomote pharmacovigilance including MedWatch, Sentinel Events Reporting Program and Medication Error Reporting Program, whereby the reporting involve both Healthcare Professionals (HCPs) and the public (Rabbur and Emmerton, 2005; Food and Drug Administration, 2019; NCC-MERP, 2019). The Canadian Adverse Drug Reaction Monitoring Program regulates the pharmacovigilance activities and pharmacist are part of this program since its inception (Rabbur and Emmerton, 2005; Cox, 2002). The Centre for Adverse Drug Reactions Monitoring (CARM) monitors adverse drug reactions in New Zealand, and pharmacists are also a part of this program (NZPhvC, 2019). In Netherlands, a spontaneous ADR reporting scheme was launched in the 1963, and since then pharmacists have been involved in the reporting of ADRS. ADR reports are submitted by doctors and pharmacists to the

Netherlands Pharmacovigilance Centre, and it has been observed that about 40% reporting is done by the pharmacists (Mes et al., 2002).

In response to the Thalidomide tragedy, Australia formally started pharmacovigilance in 1963 and formulated Australian Drug Evaluation Committee. Since then, data is being continuously collected by the Advisory Committee on Medicines, a subcommittee of the Therapeutic Goods Administration (TGA) for pre and post-marketing surveillance including pharmacovigilance (Linger and Martin, 2018). Clinicians report ADRs through an online reporting system, namely Australian Adverse Drug Reactions Reporting System or may send reports through fax, email, telephone and post. The ADRs reporting by sponsor of both the listed and registered drugs is mandatory for sponsor, while not mandatory for clinicians and consumers (Therapeutic Goods Administration, 2017). In 2015, the TGA received 17,000 reports with 4% reported by physicians, 15% from state health departments and 54% of the reports were sent by sponsors (Therapeutic Goods Administration, 2015). All data on ADRs are entered into the online database and submitted to VigiBase to detect any signals on ADR. Voluntary reporting leads to significant under-reporting of adverse events. To improve, PV system, Australia is considering introducing the Black Triangle Scheme to identify new drugs requiring more vigilance. However, underreporting remains an area of concern for Australian pharmacovigilance system (Linger and Martin, 2018).

Drug regulation in Europe (EU) started after Thalidomide tragedy in 1960s and a pharmacovigilance system for reporting of ADRs was developed to improve quality, efficacy and safety of medicines. Pharmacovigilance remains a major priority in EU drug regulatory system and spontaneous ADR reporting was introduced to provide

signals regarding hazardous medicines (Waller et al., 1996). In early 1990s, Member States of EU proposed a more closely integrated system of drug regulation, which led to the establishment of European Agency for the Evaluation of Medicinal Products, presently known as the European Medicines Agency (EMA).

In European Union, a new regulatory system is introduced that includes centralized authorization, multiple identical authorization through mutual recognition and decentralized procedures. Although pharmacovigilance in EU member states is based on individual national system, however a central coordination is provided through the EMA and Pharmacovigilance Working Party (PhVWP). The collaboration involves the agreement on standards, procedures and an exchange system for information and decision making (Bahri et al., 2007).

It is interesting to note that more than 80% of all spontaneous reports are reported from pharmaceutical industry in the United States (Gibson et al., 2008). The United States (US) Department of Health and Human Services and FDA is managing pharmacovigilance system with Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research (Food and Drug Administration, 2005). In the USA, ADRs reporting is voluntary by healthcare professionals and is done through MedWatch (Food and Drug Administration, 2019). The ADRs are reported according to the post marketing reporting to FDA, which further conveys these reports to FDA Adverse Event Reporting System and healthcare professionals, consumers, lawyers, regulated industries can report through 3500A or 3500B form to FDA (Food and Drug Administration, 2018).

The ADRs reports are evaluated by clinical reviewers from CBER and CDER. If FAERS acknowledges any safety concern, a supplementary evaluation is done, which may include studies using large databases and the record is maintained for the 10 years (Food and Drug Administration, 2018). The spontaneous reporting of an ADR remains an important part of pharmacovigilance, however it requires collaborative effort from pharmaceutical industry, healthcare professionals (HCPs), public, regulators and academia (Gibson et al., 2008).

Contrary to this, ADR reporting is scant in many low and middle come countries and it has impacted on the use of medicines, patient safety and on policy and practice (Palaian, 2018). Due to resource constraint, developing countries have had to rely on the data, available as standard drug information resources from the developed world. The differences in data due to geographical, drug utilization pattern, as well as prescription pattern makes it difficult to extrapolate the data in a developing country setting. Moreover, the drug use associated problems vary across the countries due to varied and large population sizes. Besides, lack of quality control and substandard medicines also make the safety requirement of medicines as a critical challenge (Palaian, 2018). Thus, to tackle the system and practice related issues, many developing countries have established their own national pharmacovigilance systems. These systems were established as a result of several problems including; prevalence of unique diseases, emergence of alternative drug therapies, insufficient drug information resources, variation of excipients, poor compliance of medicines, lack or absence of hospital drug and therapeutics committees, lack of computerized systems, poor medicines quality, lack of drug use pattern data (McDowell et al., 2006).

2.5 Global scenario of knowledge, attitude and practices among healthcare professionals regarding pharmacovigilance

Healthcare professional's knowledge and attitudes towards ADRs and ADRs reporting play vital role as it not only supports the ADR reporting but it also impacts HCPs' attitude towards patient care and safety. Since ADRs reporting is spontaneous and is done voluntary by healthcare professionals, improving the participation of healthcare professionals can improve reporting standards. It has been reported in studies that positive attitudes of healthcare professionals can favor ADRs reporting practices. Hence it is necessary to design strategies that modify both the intrinsic (knowledge, attitude and practices) and extrinsic (relationship between health professionals and their patients, the health system and the regulators) factors. A "KAP" study helps measure the Knowledge, Attitude and Practices of a community including healthcare professional. Thus, a knowledge, attitude, and practice (KAP) analysis may provide an insight into the intrinsic factors and help understand the reasons for the under-reporting of ADRs (Gumucio et al., 2011).

Various studies regarding determinants of reporting of ADRs worldwide showed that the higher knowledge and positive attitudes of health professionals appear to be strongly related with reporting in a high proportion of studies (Sweis and Wong, 2000; Herdeiro et al., 2005; Hazil & Shakir, 2006; Lopez-Gonzalez et al., 2009; Nichols et al., 2009).

A study conducted in 16 hospitals of China, found that HCPs including nurses and physicians had little knowledge about ADR, while only 28.5% of doctors and only 22.8% of nurses actually submitted a report. The main reasons associated with under-reporting were lack of knowledge about ADRs and the lack of knowledge regarding

voluntary reporting procedure. It was observed that the education and training of healthcare professionals was needed to improve the ADR reporting system in China (Li et al., 2004).

Herdeiro et al. (2006) found a strong association between knowledge, attitudes and under-reporting and suggested that the educational interventions designed to change knowledge and attitudes could bring important improvements in reporting (Herdeiro et al., 2006).

A study from Portugal by dos Santos Pernas et al. (2012) determined the knowledge of the pharmacovigilance among physicians, nurses and pharmacists. The lower results for knowledge showed physicians, nurses and pharmacists' lack of knowledge about pharmacovigilance and the ADR reporting processes. This lack of knowledge differs from one person to another. This is also being influenced with regards to educational level or university syllabus, and access to or interest in awareness campaigns (dos Santos Pernas et al., 2012).

A cross-sectional study conducted among physicians working in tertiary care hospital in the United Arab Emirates showed that the under-reporting of ADRs was common. However, it was observed that clinicians were willing to be trained in ADR reporting and contributing towards the pharmacovigilance programme. The physicians suggested to have workshops and training programmes on ADR reporting to overcome the under-reporting (John et al., 2012)

In Nepal, a cross sectional study conducted among Healthcare Professionals in four tertiary care hospitals found that only 20.1% had reported any ADR, though they had positive attitudes towards ADR reporting. The ADR related training and

collaboration and feedback from the national pharamcovigilance programme were mentioned as the facilitating factors for reporting. (Santosh et al., 2013)

A Nigerian study by Necho and Worku (2014) revealed that low level of knowledge was strongly related to the low level of ADR reporting among health professionals (Necho and Worku, 2014). In Malaysia, it was observed that the physicians and pharmacist had inadequate knowledge on ADR reporting. The participant's attitudes and prevalence of unsatisfactory practices contributed to failure to report an ADR even if the ADR was identified. However, educational interventions were recommended to improve the ADR reporting (Tew et al., 2016) A study by Mendes Marques et al. (2016) determined nurses' attitude regarding ADR reporting and found that nurses working in primary care were 12-fold more likely to report an ADR. A change of attitude in nurses increased the probability of ADR reporting (Mendes Marques et al., 2016). A review based on Indian pharmacovigilance system concluded that a significant gap pertaining to knowledge, attitudes and practices related to pharmacovigilance activities exist. Inadequate knowledge and training of Healthcare Professionals (HCPs), their attitudes and perceptions and problems with organizing reporting systems were found as the major hurdles of reporting an ADR (Mulchandani and Kakkar, 2019). Güner and Ekmekci (2019) identified the limited pharmacovigilance knowledge as the main reason for under-reporting of ADRs among Turkish physicians and nurses. Training activities based on the needs and preferences of HCPs and close follow-up by authorities were recommended as the main steps to improve pharmacovigilance activities. It was observed that the Healthcare Professionals (HCPs) did not know the essentials of pharmacovigilance and ADR reporting system in the Turkey and they were not aware of their role in the system (Güner and Ekmekci, 2019).

Several studies have shown a positive impact when healthcare professionals are educated on pharmacovigilance, medicines safety and adverse drug reactions. A study in India by Ganesan et al. (2017) showed that Knowledge, attitude and practices of health-care professionals can be improved following an educational interventional programme on pharmacovigilance (Ganesan et al., 2017). In another study in Brazil which evaluated the impact of an educational intervention in pharmacovigilance on the knowledge, skills and attitudes of hospital professionals showed that it improved the rate of adverse drug event reporting among healthcare professionals (Varallo, 2017). Another study by Opadeyi et al showed that the educational intervention and the use of an SMS can positively impact on healthcare professionals' knowledge and practices of pharmacovigilance (Opadeyi et al., 2019).

Following on the leads from these studies, we believe a study in Pakistani setting would provide in depth contextual data and observation. This can then form the basis to build effective interventions and strategies to improve medicines safety practices among healthcare professionals.

2.6 Healthcare system in Pakistan

Pakistan is a lower middle-income country with a population of 207.8 million and ranked as the fifth most populous country in the world (World Bank, 2019). In Pakistan, the healthcare system consists of public and private sectors, while former is a three-tiered structure, including primary, secondary and tertiary care. Primary and Secondary care centers cater the basic health needs of the population while tertiary care centers involve hospital based modern facilities. Most of the health budget goes to tertiary health care centers and the Ministry of National Health Services Regulation