PHARMACOVIGILANCE IN YEMEN

Safety monitoring of medicines: the available mechanism in Yemen

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Preface

Adverse drug reactions (ADRs) are one of the important causes of morbidity and mortality. To minimize the harmful effects of medicines, countries have developed their pharmacovigilance mechanisms. Yemen is a developing country in South West Asia with a National Pharmacovigilance Program (NPP). The current NPP in Yemen has limited coverage and receives only limited ADR reports. Though the program is successful to a certain extent, still there is a scope for improvement. This book discusses the drug regulation in Yemen, describing the existing limitations of these regulations, demonstrating the need for pharmacovigilance, and go through the different stages of pharmacovigilance activities in Yemen and finally how to foster pharmacovigilance activities to achieve the desired health care in Yemen.

We hope that this book will serve as a useful reference for those individuals and organizations who are interested in Pharmacovigilance.

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Chapter One: Introduction

1.1. Background

Every medication is potentially hazardous and can cause substantial harm to the recipient with varying degrees of injury. One of the potential hazards that accompany the use of most types of medications is Adverse Drug Reactions (ADRs). ADRs can cause short- and long-term hospitalization, morbidity, and even can lead to mortality [1].

In 1972, The World Health Organization (WHO) defined an ADR as 'any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose' [2].

During the past decade, concerns over ADRs have widened to include herbal, traditional, and complementary medicines, blood products, biological agents, medical devices, and vaccines [3]. A few other areas are also of relevance to pharmacovigilance (which the study will be focusing on later), including substandard medicines, medication errors, lack of accurate reports, use of medicines for indications that are not approved and for which there is an inadequate scientific basis, case reports of acute and chronic poisoning, assessment of drug-related mortality, abuse and misuse of medicines, and adverse interactions of medicines with chemicals, other medicines, and food. Thus, the science of safety monitoring should not be viewed only as a mere study on ADRs but rather should enclose the broad perspective of patient safety during the healthcare process.

On examining from the chronological perspective, this subject first appeared on the medical scene 50 years ago. Following the thalidomide disaster in the 1960s, which resulted in embryonic malformations in thousands of children whose mothers had used drugs during pregnancy, interest in the safety of medicine emerged.

In the 1960s, the WHO began the global monitoring of the safety of drugs and highlighted the need for pharmacovigilance because the information that was gathered before marketing any specific drug has always been incomplete [3]. In response to this, according to [4] pharmacovigilance has been established in most countries, and it is 'the science relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.' Testing the effects of medicine on animals cannot be used as evidence for toxicity in human beings, and any tests carried out on the latter during clinical trials involve only small numbers. Therefore, the effects of the medicine can only be assessed properly when the drug is widely used, and differences among countries may occur [3].

1.2. The Magnitude of the Problem

The WHO reported that ADRs are responsible for a significant number of hospital admissions with reports ranging from 0.3% to 11% of overall hospitalizations [3]. For instance, it has been estimated that over 770,000 people are injured or die each year from adverse drug events [5]. A commonly quoted meta-analysis performed in the United States (US) indicated that ADRs were between the fourth and sixth most common cause of death in 1997 [6], suggesting a major consideration for the entire healthcare system.

Hospital admissions due to ADRs have been reported as 300,000 admissions per year in the US and accounted for 6.5% of total hospital admissions [7]. In Canada, 12% of hospital admissions were reported due to ADRs [8] while in the UK 6.5% of hospital admissions were related to ADRs, with the ADR directly leading to admission in 80% of these cases [7]. Corresponding rates were 13% in France [9], 6.7% in India [10]; and the worldwide reports range at an average between 0.2-21.7% of overall hospital admissions [11].

Looking at the scenario of ADRs in developing countries, only a few studies have examined the rate of ADRs in developing countries. A prospective observational study from Iran found 11.8% of patients had experienced at least one ADR [12]. In another study from Iran, approximately 16.8% of patients had at least one ADR and 2.9% of the ADRs were identified as 'lethal'[13].

A study from South India reported an overall incidence of 9.8%. This included 3.4% ADR-related admissions and 3.7% of ADRs that occurred during the hospital stay [14]. In Nepal, the prevalence of ADRs was 0.86%, the male to female ratio was 0.85, and 10.81% of the ADRs were considered 'severe' [15]. The mortality due to ADRs is also a substantial problem. For instance, deaths due to ADRs in the US amount to 160,000 deaths annually [16]; in the UK, the corresponding figure was 1044 deaths [17].

In France, ADRs accounted for 0.12% of deaths [4].

The above statistics on hospitalization and mortality due to ADRs highlight the fact that it is essential to monitor ADRs to minimize or prevent harm to patients arising from their medicines; to detect ADRs before they are clinically manifested, and to obtain more knowledge to ensure the safe use of medicines, and to assess the harms, benefits, and risks of available drugs [3].

1.3. What Is ADR?

There has been a growing trend in recent years on reporting of the ADRs. The majority of the drug regulatory agencies around the world have developed a reliance on the detection and reporting of suspected ADRs for improving medication safety in the population. An adverse event (AE) connotes 'any untoward medical occurrence that may arise during the treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment'. Perhaps, a better definition compared to WHO (2002) and the new Adverse Drug Reaction definition was given by Edward and Aronson as: *'*An appreciable 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 regime or withdrawal of the product' [18].

ADRs are known to cause morbidity, mortality, increase the duration of hospital stay, and the cost of hospitalization. Lazarou et al. (1998) even pointed out that ADRs related to prescribed medicines are among the fourth to sixth most common causes of deaths in the US. Statistics show that 300,000 patients are hospitalized every year due to ADRs in the US [6] Shapiro (1971) has reported 160,000 deaths in the US annually due to ADRs and this figure may not be very different from what happens in other countries [16]. Moving to the world at large, Einarson (1993) draws attention to the fact that 0.2-21.7% of hospital admissions are due to ADRs [11].

ADRs are classified into four types, which are adapted from the original classification by Rawlins (1981): Type A is 'Augmented,' Type B 'Bizarre,' Type C 'Cumulative,' and Type D 'Delayed.' A deeper understanding of the nature of ADRs reveals them to be 'dose-related', 'time-related', and 'susceptibility-based'. As per the Dots classification system of ADRs, which is based on the time course and susceptibility as well as dose responsiveness, ADRs that are dose-related contain some toxic effects, where the ADRs occur at doses higher than the normal therapeutic dose. Some ADRs may happen at standard therapeutic doses and the higher susceptibility reactions occur at subtherapeutic doses in susceptible patients. The time-related nature of ADRs is seen in the ADRs that occur at any time during the treatment given, causing various reactions [19].

Some ADRs are categorized as 'rapid reactions' that occur when a drug is administered too fast. Similarly, 'early reactions' occur early on in the treatment and then abate with continuing treatment. 'Intermediate reactions' occur after some delay, but if the reaction does not occur after a certain time little or no risk exists. The 'late reaction', in turn, suggests that the risk of

ADR increases with continued or repeated exposure, including withdrawal reactions. 'Delayed reactions' occur after some time following exposure, even if the drug is withdrawn before the ADR occurs. Some individuals are known to possess a raised susceptibility towards the occurrence of ADRs. The various factors that are associated with increased susceptibility of ADRs include genetic variation, age, sex, altered physiology, exogenous factors (interactions), and disease [20].

The American Food and Drug Administration (FDA) defines a serious adverse event as one when the patient outcome is one of the following:

- Death.
- Life-threatening.
- Hospitalization (initial or prolonged).
- Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities, or quality of life.
- Congenital anomaly.
- Requires intervention to prevent permanent impairment or damage.

1.4. Introduction in Pharmacovigilance

Medicines have been developed and used for centuries, but only in the 1960s as it deemed necessary to closely control the quality, efficacy, and safety of medicines before making them available to patients. Pharmacovigilance has a role in this context.

Before a medicine is marketed, extensive clinical studies are conducted. Nevertheless, these studies have limitations due to the strict and standardized conditions in which they are conducted. Once the medicine is marketed, it is used by a more heterogeneous population (e.g. patients with important morbidity or patients taking other medicines,

children, or elderly people), in other circumstances than the ones of the clinical study, sometimes by millions of patients and for years.

At the beginning of the ’60s, it became apparent that the medicine Softenon® (thalidomide) was causing congenital disorders (resulting in shortened or missing limbs) among children whose mothers had used the medicine during pregnancy. This medical disaster led to a global awareness that medicines can produce unexpected adverse effects. In 1968, the WHO established an international pharmacovigilance-program that has been executed since 1978 by the international center for pharmacovigilance that centralizes data about adverse effects collected by national pharmacovigilance centers.

Some rare adverse effects or adverse effects that occur late are often only detected at that moment. For this reason, it is necessary to report adverse effects to the Centre for Pharmacovigilance for medicines for Human use once a medicine is marketed and used under real circumstances

1.5. Definition of Pharmacovigilance

Pharmakon means a drug, Vigilance means an open eye. Pharmacovigilance (abbreviated PV or PhV) is the science and activity relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible medicine-related problems. In 2005, 78 member countries are participating in this Programme and the last decade has seen the participation of numerous developing countries. The program functions based on national pharmacovigilance centers coordinated by the WHO Programme for International Drug Monitoring, which consists of the WHO Collaborating Centre for International Drug Monitoring, Uppsala, and the Pharmacovigilance Department of WHO, Geneva.

1.6. Purposes of Pharmacovigilance

Recently, the concerns of pharmacovigilance have been widened to include herbal, traditional, and complementary medicines, blood products, biologicals, medical devices, and vaccines. Many other issues are also of relevance to the science of pharmacovigilance. These include substandard medicines, medication errors, lack of efficacy, use of medicines for indications that are not approved and for which there is an inadequate scientific basis, case reports of acute and chronic poisoning, assessment of medicine-related mortality, abuse and misuse of medicines, and adverse interactions of medicines with chemicals, other medicines.

1.7. The Need for Indigenous Pharmacovigilance Programs in Every Country

There are differences among countries, or more precisely among regions within a country, in the occurrence of ADRs and other drug-related problems. This may be claimed to differences in disease, prescribing practices, genetics, diet, traditions of the people, drug manufacturing processes used which influence the pharmaceutical quality and composition drug distribution and use including indications, dose, and availability; the use of traditional and complementary drugs, which may pose specific toxicological problems when used alone or in combination with other drugs.

Data derived within a country or region may have greater relevance and educational value which probably would encourage national regulatory bodies towards proper decision-making. Nonetheless, applying information obtained from another country (e.g. the country of origin of the drug) might not be relevant as well as cannot be applied to other parts of the world where circumstances might differ. Therefore, drug monitoring is of tremendous value as a tool for detecting ADRs and

specifically about counterfeit and substandard quality products. ADR monitoring is to assure that patients obtain safe and efficacious products.

1.8. Lack of Monitoring Adverse Drug Reactions in Developing Countries

Looking at the scenario of ADRs in developing countries, only a few studies have examined the rate of ADRs in those countries [12-15].

While major advancements of the discipline of pharmacovigilance have taken place in developed countries, not much has been achieved in developing countries which still have a major weakness in mechanisms and procedures of ADRs reporting and other pharmacovigilance activities and difficulties to monitor properly the harmful effects of medicines. However, in some countries, there are some efforts to apply the pharmacovigilance activities by establishing pharmacovigilance centers to ensure the safe use of medications.

There is a little effort in developing countries to collate, aggregate ADRs, and analyze the reports in public health programs because drug safety did not come in the top priorities of health in developing countries. ADRs problems in the developing countries are very serious, unknown, and not disclosed exposing a huge number of people to risk.

New drugs are reaching developing countries in greater numbers and more quickly so the burden of adverse events that are resulting from poor quality, ADRs, and medication errors may affect achieving the full benefit of these new drugs. In addition to that, most drugs are manufactured in developed countries and have a safety profile that may not be applicable in developing countries, which can differ in genetic and social differences.

Considering the monitoring of ADRs is the first step to help in applying all other pharmacovigilance activities such as analyzing and

assessing these events and study the association between these events and the drug. Furthermore, monitoring ADRs will help both researchers and regulatory bodies to conduct pharmacoepidemiological evaluations and studies to make sure of the safety profile of these drugs in real-world patients, which cannot be achieved through pre-approval clinical studies. Thus, the aforementioned pharmacovigilance activities may not be easy to be performed in the absence of ADRs monitoring which we lack in most developing countries.

Several challenges face running good pharmacovigilance activities in developing countries including the following:

1. Lack of knowledge and awareness about the importance of drug safety among responsible authorities
2. Lack of funding to run, establish, and ensure a good atmosphere for pharmacovigilance centers and create a safety culture among health professionals and the public. Pharmaceutical companies in these countries do not perform the pharmacovigilance activities and if they do, they do not do it in the right way.
3. Weak regulations.
4. Low literacy levels.
5. Low awareness and poor knowledge among health professionals and the public regarding ADRs reporting and pharmacovigilance as it is shown in some studies conducted in the developing countries.
6. Communication difficulties between healthcare professionals, regulators, and pharmaceutical companies.
7. Counterfeit drugs are a very important and underreported problem in developing countries.

8. Self-medication which makes reporting ADRs to health professional or pharmacovigilance centers impossible.
9. Traditional and herbal medications are widely used in developing countries without medical supervision.
10. Lack of expertise and training programs in developing countries.

All stakeholders (regulatory bodies, pharmaceutical companies, and healthcare professionals) need to start doing their tasks regarding monitoring ADRs. Healthcare professionals need to understand the importance of reporting ADRs and to be part of their practice as it could prevent harm from affecting their patients. Pharmaceutical companies need to work with regulatory bodies to enhance the culture of reporting ADRs among healthcare professionals by giving education materials and scientific workshops for them. Further, reporting all ADRs within the time limit of the pharmacovigilance regulations and follow up with the healthcare professionals as well as regulatory bodies. Finally, the regulatory body, which has the main responsibilities, cooperation with the pharmaceutical companies, is very important to facilitate all obstacles for them and clear guidelines to be followed should be available. Further, regulatory bodies need to evaluate and analyze the

Chapter Two: Current Pharmaceutical Situation (Services) in Yemen and Future Challenges

2.1. Health Status and Demography

Yemen is an Arab country located in the southern Arabian Peninsula with a population of 24 million, 70% of whom live in rural areas. Yemen divided administratively into 24 governorates and Sana'a Capital Trust. Each governorate subdivided into several districts. Yemen has not been able to escape the many chronic diseases that have also plagued other Arab countries and the developing world in other regions. It has been known to have a high incidence of both communicable diseases (malaria, tuberculosis, schistosomiasis, sexually transmitted diseases, and vaccine-preventable diseases) and non-communicable diseases (such as cardiovascular diseases, renal problems, cancer, and eye diseases). As if this is not enough, Yemen also displays certain factors of lifestyle that can pose risks or are hazardous to the people (the factors include tobacco use, 'qat' chewing, malnutrition, injuries, and accidents) and inadequate necessary sanitation (especially water sanitation). Unfortunately, these are steadily increasing. The health situation in Yemen is acknowledged as the least favorable in the world. Low birth weight has been known as one of the leading contributors to Yemen's very high infant and under-five mortality rates The causes for this are three-fold- poverty, closely-spaced pregnancies, and low health awareness. The high fertility rate is also another issue among Yemeni women. Higher fertility would add more pressure on a woman's body and thus, they run the risk of being subject to potential death or mortality. This is exacerbated by the fact that Yemen is poor in resources and being over-populated this would definitely be a big issue to address. Other factors including not being able to access healthcare, and not being able to afford healthcare expenses, parents not being too educated and poor access to the basic necessities, like water and sanitation are also responsible.The most common and serious health conditions Yemen faces are diarrhea, malnutrition, complications of pregnancy, acute respiratory infections, and malaria. AIDS is becoming increasingly prevalent, and non-communicable conditions such as cancer, heart disease, and trauma are also on the rise[21].

Table 2.1. The Basic Indicators of Healthcare in Yemen.

Under-5 mortality rank	43
Under-5 mortality rate (U5MR), 1990	125
Under-5 mortality rate (U5MR), 2012	60
U5MR by sex 2012,male	64
U5MR by sex 2012,female	56
Infant mortality rate (under 1), 1990	88
Infant mortality rate (under 1), 2012	46
The neonatal mortality rate of 2012	27
Total population (thousands) 2012	23852,4
Annual no. of births (thousands) 2012	752,2
Annual no. of under-5 deaths (thousands) 2012	43
GNI per capita (US$) 2012	1110
Life expectancy at birth (years) 2012	62,9
Total adult literacy rate (%) 2008-2012*	65,3
Primary school net enrolment ratio (%) 2008-2011	76,4

Source: [21] http://www.unicef.org/infobycountry/yemen_statistics.html#121

2.2. Health Care System

The health care services (either public or private) are mainly centralized in major cities; though primary health units/centers, polyclinics and hospitals are scattered throughout the country. The health care system consists of a public and a private sector. There are three levels of health care. The first level is primary health care that focuses on primary health programs and provides the first level of care. Primary health care facilities consist of health units, health centers, and polyclinics. Primary health units commonly have one medical assistant or nurse and/or midwife. Primary health care centers normally have one or two physicians, nurses, a laboratory, and some diagnostic facilities. The second health care level is secondary health facilities which consist of regional hospitals, specializing in curative services. The third one is the tertiary health facilities which include the national hospitals offering specialized care, and they are university-based hospitals. The entire healthcare system in Yemen is monitored by the Ministry of Public Health and Population (MOPHP) which is directly responsible for the health sector and this sector takes up the largest percentage of Yemen's public employees. As it is in most other countries, Yemen does not escape the issues of not having adequate numbers of staff, having to deal with poor construction and organization, poor quality healthcare services, not having enough medicines that are deemed essential for patients, and insufficient issues of budget and Government funding.It can be safely summarised that the health services in Yemen have been outgrown by the exponential population growth. With prominent morbidity and mortality from various diseases and with high levels of malnutrition prevailing, and the higher rates of fertility reported. Therefore, the Yemen health care system has still a long way to go [22].

➢ Overview of Yemeni Pharmaceutical Sector Before the War:

The situation of the health and pharmaceutical sectors before the war was less than satisfactory; however, it was better than at the current time. The National Health Policy (NHP) which was updated in 2010 and National Medicines Policy (NMP) which was updated in 1998 were not applied in practice (MOPH). Availability and affordability of essential medicines/health technologies are considered as a fundamental health right, but though they have been documented in the national regulation the situation in practice is far from satisfactory [23].

The system of medicines donation for essential medicine did not offer a persistent supply and was plagued with continuous shortages. The Ministry of Public Health and Population (MOPHP) did not provide a good national health policy. There is neither a corresponding formal implementation plan nor clear responsibilities and the policy has not been evaluated. It also does not cover important areas such as pharmacovigilance, human resources development, traditional medicine, monitoring and evaluation, and research. Medicines trade and manufacture did not consider Intellectual Property (IP) Rights due to the absence of international agreements. On th e positive side locally, manufactured medicines were proven to have good quality [23].

Availability and affordability of medicines in public pharmacies were poor compared to their availability in private pharmacies, also most medicines were not affordable for the majority of citizens. Medicines prices ranged from low to high according to the brand name. low-price medicines were relatively affordable to common people. Medicine smuggling was also a critical issue. Government reports indicated that more than 10 % of medicine were counterfeit [24]. However, other reports showed the percentage to be closer to 60% [25]. Counterfeit medicines find a fertile market in Yemen due to the poverty of Yemeni citizens, lack of awareness of the dangers of these drugs, and lack of strict laws that penalize the smugglers.

The medicines regulatory system is overseen by the Supreme Board of Drugs and Medical Appliances (SBDMA) which is responsible for medicine regulation in Yemen such as approving marketing, trade, and industrial regulation, providing authorization for medicines, medicine manufacturers and suppliers, regulating the medicine market and monitoring the quality of and supporting pharmacovigilance of medicines and medical appliances. In 2007, about 9,500 pharmaceutical products were registered in Yemen. The duties of the government pharmaceutical inspectors, such as checking of the building used for the pharmaceutical activities, local producers, private suppliers, and retail distributors were infrequent [26]. Local pharmaceutical manufactures met only 10-20% of the national requirements (SBDMA). The medicines provided to the public sector were centrally procured by the Central Medical Stores in Sana'a, the capital, which in turn supplies the medicines to the governorate's main stores. In 2011, there were 3,315 pharmacies (licensed for pharmacists) and 4,133 drug stores (licensed for pharmacy technicians) [27]. However, rational use of medicines was poorly followed and pharmacovigilance knowledge was low among physicians, pharmacists, nurses, and medical assistants. Several other pharmaceutical-related issues such as drug trafficking, substandard drugs, inappropriate and irrational use of drugs, importation of redundant drugs, and medical misuse were common. Pharmacies were often manned by pharmacy technicians and untrained dispensers with only a few pharmacies being managed by qualified pharmacists.

It is clear that despite the government efforts to promote and develop the pharmaceutical sector, it was poorly developed before the war. There were plans and recommendations to improve the current health system such as updating the pharmaceutical policies and regulations, providing adequate education and knowledge about the rational use of medicines and pharmacovigilance, controlling drug smuggling, improving the quality of pharmaceuticals, and increasing the percentage of requirement met by local industries. Unfortunately, the war and siege made the situation go from bad to worse.

- **The Current Situation of The Yemeni Health and Pharmaceutical Sector:**

Life in Yemen has become catastrophic after almost four years of conflict. Yemeni people have been facing various humanitarian crises. Almost 80% of Yemeni people require humanitarian assistance because conflict and siege have destroyed the economy. Almost 81% of Yemeni people live below the poverty level, basic foods are unaffordable and people are at risk of malnutrition [28].

The active conflict, displacement, and economic decline also disrupted the basic essential services resulting in a shortage of electricity, fuel, and water supply. In 2019, only 51 percent of health facilities are fully functional and over two-thirds of Yemenis lack adequate access to clean water, sanitation, and hygiene (WASH) [28].

The decline in WASH and health services was the major driver of the cholera epidemic with more than 1 455 585 suspected cholera cases reported from October 2016 to January 2019 with 2,906 associated deaths [29].

There is also a resurgence of previously controlled diseases and an increase in the prevalence of endemic communicable diseases. Diphtheria has been reported in many governorates according to the WHO [30], measles [31], and pertussis cases were also reported, [32] which is due to the reduction in vaccination rates since 2013 [33].

There must be efforts to keep the country clean by activating the municipal and other services and providing access to clean drinking water to all parts of Yemen or else Yemeni people will continue to suffer from the ongoing cholera epidemic. United Nations Office for the Coordination of Humanitarian Affairs (UN OCHA) reports that 16 million Yemenis currently lack access to safe water and sanitation. In August 2018, local authorities organized an oral cholera vaccination campaign as mentioned on the web site [34].

There is a high probability of a possible outbreak of polio and other childhood diseases if vaccines remain inaccessible to the population [35].

Dengue fever is endemic in Yemen, with epidemics in several governorates through the preceding 10 years. However, on the positive side, there has been a partnership between the WHO and the health care system to provide essential therapy, health workers to manage diseases, and information campaigns to reduce the causes of disease spread as run in its web site [22].

According to a study conducted in Aden city from April to August 2015, respiratory infections, gastroenteritis, and trauma were the most prevalent health problems [36].

The continuation of the war has led to an increase in the number of wounded and disabled people increasing the burden on hospitals. Mental illness as a natural reaction to the horrors and woes of the war is added to the burden of physical disabilities. Currently in Yemen, the non-communicable diseases kill more people than war-related injuries and account for 57% of all mortality in Yemen [28], however, non-communicable and mental health services are fully available in only 21% of health facilities, while 28% of health facilities are lacking these services [37].

Due to the destruction of infrastructure, lack of clean, drinking water, deprived sanitary situation, and deficiency in access to oral rehydration salt (ORS) there is an increased frequency of diarrhea [38].

Internal displacement plays an important role in increasing the prevalence of infectious diseases due to overcrowding and lack of hygiene, as well as, the transmission of infections by individuals from their home area to the areas to which they have migrated, and exposure to new diseases they have not experienced before migration and have no immunity for.

To deal appropriately with the health crisis, there must be an adequately functioning health and pharmaceutical sector. However, there has been a severe shortfall in the supply of essential medicines and

vaccines. The ongoing conflict, siege, and restriction on imports affect both the availability and quality of medicines. Drug supply is limited to private pharmacies, the aid provided by humanitarian organizations, and assistance from Yemenis living abroad. The services provided by government hospitals and health care centers are collapsing due to their destruction, staff deficiencies, or safety problems. According to a study carried from September to November 2016, the price of medicines has increased up to 71% and about 80% of medicines enter into the country via illegal routes and about 40% were fake or of low quality [39].

There is a serious shortage of essential medicines for both acute and chronic diseases and also of life-saving medicines as mentioned in their websites [40]. Some medicines have disappeared from the market because of the difficulty of importing them and the high taxes imposed on pharmaceuticals. The availability of outpatient services with all essential drugs is limited to 18% for the primary care facilities and 46% for hospitals.

The frequent electricity shortage results in poor storage conditions which consequently affect medicine stability and efficacy. All these factors reduce the public trust in the health system, medicines, and vaccines, even if the vaccine cold chain is functioning and there is a proper import system, which has negative consequences on vaccination acceptance. There have been many reports of violent attacks against health workers [41].

Lack of security has also led to the undermining of health care services. In addition, a shortage of electricity, fuel and water supply, and lack of transport hinder the facilities provided by governmental health care centers. About 50 % of the health care centers in Aden city were considered functionally inefficient [39]. Many hospitals and health centers over the whole country either fail to function at all, function poorly, or were temporarily closed, making the situation difficult.

The destruction also included pharmaceutical factories. Most factories are located in Sanaa which is always under frequent aerial bombardment leading to a shortage of locally produced medicines, and migration of staff to safer places has also weakened the production capacity of working factories. As a result of the weak purchasing power of the Yemeni citizen, some pharmacies have been forced to shut down. The difficulty of living a decent life in Yemen and the deficiency of access to sources of livelihood has forced young people to migrate abroad. Youth migration led to a shortage of workers in factories, pharmacies, and other vital facilities. Rising fuel prices, scarcity, lack of electricity, difficulty in importing raw materials, and the collapse of pharmaceutical machines have weakened the production capacity of factories.

In short, the health and pharmaceutical sectors are in a deplorable condition. The economic and political factors are taking their toll on the Ministry of Health's ability to fund the continued operation of the facilities and individuals have difficulty in paying to access these services. Consequently, millions of people lack access to health care and the conflict does not seem to be ending soon.

The war in Yemen triggered the WHO and the Yemeni authorities to list and act on certain major concerns:

(1) The large gaps in health care provision.

(2) The supply of medicines and medical equipment is disrupted.

(3) Patients who suffer from chronic illnesses are not getting proper treatment.

(4) Higher rates of mortality of mothers and children.

(5) Increasing resources needed to treat mental health.

(6) More need for surgical procedures, intervention, and rehabilitation for conflict-related injuries.

(7) Higher risk of communicable diseases.

The WHO in particular seeks to support the Ministry of Health by coordinating its efforts with 44 other agencies to meet the health requirements of the dying population, and particularly those directly affected by the conflict. The Health Cluster in Yemen seeks to reach millions of people with various kinds of vulnerabilities needing health assistance. Its priorities are as follows:

- Sourcing and distribution of medical supplies and equipment.
- Addressing critical cases of non-communicable diseases
- Vaccinating against measles, polio, and rubella.
- Preventing vector-borne diseases, like malaria.
- Having a comprehensive primary healthcare system.
- Lending support to conflict-related injuries.

Thus, the war in Yemen has brought together relevant players to revive the healthcare, social and environmental circumstances in Yemen.

The authorities have recognized that the health workforce development needs to be strengthened and supported in Yemen, and several proposals have talked about supporting the post-conflict return of health workers (from both within the country and abroad), through a combination of links with host countries, negotiating a temporary release from contracts for diaspora workers, and better pay. However, there was also recognition of major health system weaknesses pre-conflict centered on accountability, transparency, and corruption that have now been complemented through the fragmentation of the government and the pitfalls in financing. Participants agreed that grass-roots leadership structures would likely play an important role in filling the governance gap during any recovery period, and would need to be supported through better training, and alternative financing models.

Next, trauma-related illnesses represent a substantial part of the burden on health services and will do so for the foreseeable future – both acutely and chronically (through support with prosthetics and long-term physical and psychological rehabilitation). Nonetheless, there is also an increasingly urgent need to build effective primary health care and preventive care systems to reverse increases in child and maternal mortality, including a series of efforts to tackle malnutrition. Work to develop tailored basic care packages reflecting complex local service challenges and new realities on the ground in Yemen are urgently needed. Finally, there was widespread recognition of the critical importance of accurate health information. Participants agreed that without this, effective reconstruction planning would be impossible, and urged greater attention to surveillance of primary causes of mortality, using community-based information gathering approaches; strengthening existing health surveillance systems; and setting up surveys to track health needs in the worst affected areas of the country.

2.3. National Policy Issues

A National Health Policy (NHP) does exist in Yemen, and it was updated in 2010 unfortunately the corresponding implementation plan does not exist. Similarly, the National Medicines Policy (NMP) document also exists in Yemen which was updated in 1998 [42]. In brief, these two policies exist but are neither structurally implemented nor regularly monitored and evaluated. In general, there is no formal implementation plan and there are no clear responsibilities.

In terms of drug distribution for health care purposes, Yemen should consider the drawing up of a concrete and updated statement of NMP such has been adopted in many other WHO member states. Next, a policy relating to clinical laboratories does not exist either. Access to essential medicines/health

technologies as part of the fulfillment of the right to health is recognized in the constitution or national legislation but they are not fulfilled. Unfortunately, there are no official written guidelines on medicine donations. It is important to establish a well designed, well managed, and cost-effective supply system to increase access to essential medicines; maintaining constant supply, and minimizing medicine losses. In sum, there is no national good governance policy in Yemen and this is probably why Yemen's MOPHP have to take measures to ensure clear-cut guidelines and policy are reformulated and re-outlined. They have to be thorough, covering all aspects of healthcare and the guidelines have to be delivered efficiently and effectively to the authorities of the three levels of the healthcare system in Yemen before they can be implemented in different health care facilities, in both the public and the private sectors. It is worth to mention that the National Health Strategy (NHS) 2010-2015[42] has stated that: "The MOPHP has exerted some great effort towards improving the health conditions for the people through its constant attempts to *reform the health sector and modernize it. The policies and strategies that have been adopted by the Ministry since the end of the 1990s were an obvious extension of the issues adopted in the First National Conference for Health Development in 1994. This strategy hasn't ignored or canceled the accomplishments of the previous strategies but rather it was built on their success and is having its priorities updated in line with the national, regional, and international developments bearing in mind the national and local characteristics and inconsistency with the various economic, social, political and geographic conditions".*

2.4. Medicines Trade and Production

The World Trade Organization (WTO) does issue legal provisions and grant patents to medicine manufacturers, but since Yemen is a new member of this organization (2014), the provision and patent do not exist in the country. As is the case with any agency which should be responsible for managing and enforcing Intellectual Property (IP) Rights. Yemen Pharmaceutical Country Profile (2006) states that due to this, there has been no clear vision about IP Rights since the negotiation with international agencies is still in progress. The profile further adds that there are some legal provisions for the connection between patent status and marketing authorization, there has yet to be a similar provision for data exclusivity for pharmaceuticals and patent term extension. Yemen is also lagging, in terms of initiatives to manage and apply for the IP Rights towards promoting public health [43].

products have been proven to be of good quality, the Yemeni pharmaceutical industry still necessitates a great deal of serious attention and improvement from various angles, such as production, manufacturing, knowledge, attitude and behavior, policy-making- all together to elevate people's awareness of the nature of medicines, the use of medicines, and for the betterment of the public's health status. Thus, on the surface, we can say that the medicine trade and production in this country have to be better monitored and guided, to improve the quality, safety, and efficacy, also to reduce the cost and to curb the adverse effects of pharmaceutical products.

2.5. Medicine Regulation

In general medicine regulations and legislations aims to ensure the quality, safety, efficacy of medicines, and accuracy of medical information. It is developed, implemented, monitored, and re-enforced by Medicine Regulatory Authority (MRA). The government of Yemen granted the power of responsibility to the MRA. MRA is responsible for the registration of medicines; importation, distribution, and sales of medicines; medicine promotion; licensing of pharmaceutical establishments, their staff, and performance; pharmaceutical quality assurance; commitment to Good Manufacturing Practice (GMP) and regulation enforcement. The SBDMA is the main MRA in the country. It is a semi-autonomous agency concerned mainly with authorizing marketing, importing, and manufacturing control; providing licenses for medicines, medicine producers, and wholesalers; controlling the medicine market, and controlling the quality and pharmacovigilance of the imported medicines and medical appliances. In the last five years, the medicines regulatory system has been placed under proper assessment. The SBDMA receives funding from the government budget but it also retains its revenues from regulatory activities.

In Yemen, marketing authorization for all pharmaceutical products is required. Since mutual recognition mechanisms do not seem to be available, publicly available criteria have been adopted to assess applications for marketing authorization of the products. Yemen Pharmaceutical Profile, 2006 states that there were 9,500 pharmaceutical products registered in Yemen in 2007. However, one apparent weakness is that the MRA fails to distribute a list of the registered products, updating the names of the products regularly, to know about the authorized products that are officially available in the country.

The Profile further reveals that there is a guide for the registered pharmaceuticals but it has not been updated for more than a decade. Registration and authorization should have made the public feel 'safe' about using the medicines that are suitable to their health complications and needs, but the seemingly lackadaisical attitude of the authority regarding updating the medicines and pharmaceuticals marketed have created loopholes in the healthcare system in Yemen. Similarly, even though legal provisions exist to allow the appointment of government pharmaceutical inspectors and to allow them to check premises in which pharmaceutical activities are performed, local manufacturers, private wholesalers, and retail distributors have claimed that inspections have been infrequent and there have been suggestions of contradiction between the responsibilities of the MRA and those accountable for the pharmaceutical affairs in the MOPHP.

2.6. Medicine Financing

As has been seen earlier, Yemen is a country challenged with limited economic and social development. Its health indicators are some of the lowest globally, and improving them is a very difficult battle. In 1995, the Government launched an economic reform program with support from the World Bank and the International Monetary Fund (IMF).

The Government revenues are 37.7 percent of Gross Domestic Product (GDP), over 68 percent from oil, 24 percent from taxes, and the remainder from other sources [43]. The external debt to GDP ratio is 74.9 percent (before rescheduling) and gross official reserves account for about 4 months of imports. Another challenge to the Government's efforts to strengthen its economy came in 1998 following a dramatic drop in oil prices. The resulting 15 percent across-the-board cut in the public sector budget, further tightened scarce resources for the health sector. As a result, public spending on health is currently about 2 percent of GDP and 4.8 percent of total government

expenditure - the lowest per capita health spending in the region [43]. Limited public resources and poor health indicators are catalysts for rethinking of the health strategy by the MOPH in partnership with the World Bank and other key donors.

Potential sources of funds for public pharmaceutical procurement include government financing, user fees, health insurance, community co-financing for health facility visits, diagnosis and treatment, and donor financing. These options vary in terms of efficiency, equity, and sustainability. The most important considerations for public procurement are total funds available, adequate access to foreign exchange, and the regularity with which funds are available. It is the responsibility of government, policymakers, and senior managers to establish appropriate and reliable funding for public drug procurement as a high priority, and to implement mechanisms which provide adequate funding on time to support public sector procurement.

Looking specifically into Yemen, there are six major sources of funds for government health spending:

1. The central MOPHP budget;
2. Foreign assistance;
3. Governorate health budgets; (there is a small budget allocated to each governorate to cover some of their health expenses)
4. The Social Fund for Development (provided by the Prime Minister's Office);
5. The Public Works Project (under the Ministry of Planning & Development);
6. The Ministry of Finance, which directly funds the central MOPHP budget, the governorate budgets, as well as Al-Kuwait and Al-Thawra Hospitals in Sana'a and the SBDMA (institutional budget).

2.7. Pharmaceutical Procurement and Distribution in The Public Sector

Yemen is a member of the Arab Union of the Manufacturers of Pharmaceuticals and Medical Appliances and ranks 11th among Arabic countries in medicine production. Yemen spends about US$263 million a year on pharmaceutical products, according to the SBDMA [24].

Most of this expenditure is spent on importing medicines from 50 countries through 400 licensed importers, as local pharmaceutical plants produce only 10–20 percent of Yemen's requirements. There are about 500 foreign pharmaceutical companies and more than 13,000 brand and generic medicines registered in Yemen. In 2012, the MOPHP and the SBDMA started a new policy to ensure the quality of medicines in Yemen [24].

In 1964, the Yemeni government initiated a joint v enture with private investors in establishing the Yemen Drug Company (YEDCO). This company started in marketing pharmaceutical products. The company imported drugs from foreign companies and marketed and distributed them in local pharmacies and drug stores. A few decades down the line, YEDCO took a step forward by starting its first pharmaceutical factory in Sana'a for producing pharmaceutical products. The second pharmaceutical company, Shibapharma was established in Sana'a 29 years after the Yemen Drug Company. ShibaPharma products are sold in Yemen and even exported to Middle Eastern and African countries.

The dispensers in pharmacies are mostly not pharmacists, and a journal has revealed that a few pharmacies even use the old versions of the British National Formulary (BNF) or the East Medical Index [25].

This implies that poor quality and out-of-date drug information resources in pharmacies can affect the quality of the information provided

to patients and prescribers, and the consumers will not be updated regarding new information on pharmaceutical drugs they are purchasing.

In a manual of the WHO (1999) entitled *"Operational Principles for Good Pharmaceutical Procurement", it has been mentioned pharmaceutical procurement is a complex process involving many steps, agencies, ministries, and manufacturers"* [44].

Existing government policies, rules, and regulations for procurement as well as institutional structures are frequently inadequate and sometimes hinder overall efficiency in responding to the modern pharmaceutical market. There are many steps in the procurement process. No matter what model is used to manage the procurement and distribution system, efficient procedures should be in place: to select the most cost-effective essential drugs to treat commonly encountered diseases; to quantify the needs; to pre-select potential suppliers; to manage procurement and delivery; to ensure good product quality, and to monitor the performance of suppliers and the procurement system. Failure in any of these areas leads to a lack of access to appropriate drugs and to waste of resources. In many public supply systems, breakdowns regularly occur at multiple points in this process.

In Yemen, drugs supplied to the public sector are procured through international tender and rarely by limited competitive tender or local purchase from local agents. Procurement is based on the prequalification of suppliers. Public sector procurement in Yemen is both centralized and decentralized. The government supply system department in Yemen has Central Medical Stores at the national level in Sana'a Capital Trust which, is also known as Sana'a central medical stores. There are another 4 regional public warehouses responsible for the storage and distribution of medicines, medical appliances, and medical supplies. Each regional store

stores and distributes medicines, medical supplies, and medical appliances to the public MOPHP stores in several governorates that are located near to it. The governorate main stores distribute medicines, medical appliances, and medical supplies to the MOPHP health facilities in the governorate. There are 95 national guidelines on Good Distribution Practices. In Yemen a licensing authority that issues Good Distribution Practices licenses does not exist, notwithstanding.

2.8. Selection and Rational Use of Medicines

In Yemen many papers and documentation, regarding pharmaceutical regulation and procurement commonly exist, and yet when it comes to the implementation, updating the policies and information the scenario is poor. The National Essential Medicines List (NEML), for instance, was last updated in 2009 [42] and we are sure that a lot of the medicines would have been reexamined and revised since then.

However, the last alignment between the List and the Standard Treatment Guidelines (STG) was reported in 2010. There is no public or independently funded national medicines information center functioning to provide medicinal information or findings to prescribers, dispensers, or consumers. Public education campaigns are also lacking. For the past two years, there have been no campaigns aiming to educate the public on using medicines rationally.

Not only that, surveys which might be another medium of information to the public at large have also not been conducted. No national program, or committee, seeking to monitor and promote rational use of medicines seems to be under consideration by the MOPHP. It is equally disappointing that Yemen has no regulations which necessitate

hospitals to organize/develop committees concerned with Drug and Therapeutics, and subsequent adherence to STG also does not exist, or in some cases, have become obsolete. For physicians, nurses, medical assistants, and other health staff, pharmaceutical issues are not detailed and explained to them as a part of continuing education. Even if continuing education is mandatory, pharmaceutical concerns have sadly been underestimated and are not included.

This brings us to the next issue- pharmacovigilance. Pharmacovigilance is defined by the WHO as the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any possible drug-related issues. Drug regulatory mechanisms were strengthened following the 1961 tragedy involving thalidomide [45]. One thing that had seemingly escaped the awareness of the people at the time was how prescribing drugs for off-label purposes or in simple words, for purposes other than those intended and prescribed for was (and still is) a common practice in a lot of countries today. Little did they know then that some drugs can cause adverse reactions which are sometimes severe and even detrimental and fatal. In 1961, it occurred to the physician who had first introduced thalidomide to his pregnant patients that it was the same product that might have caused severe birth defects in the babies he had delivered. The drug interfered with the babies' normal development, causing them to be born with phocomelia, resulting in shortened, absent, or disfigured limbs. Through confirmation of the effects it had on the babies, the drug was banned in most countries.

In Yemen, the monitoring of adverse drug reactions was started by the establishment of a pharmacovigilance center in 2011 by the SBDMA [24]. So far there is no published information about its work, number of reports, and how they are processed. Also, problems related to drug smuggling, counterfeit drugs, improper and irrational use of drugs, importation of unnecessary drugs, and medical errors widely existed.

Academics from the Faculty of Pharmacy at Aden University decided recently, with responsible officers from SBDMA in Aden, to initiate a pharmacovigilance program in Yemen, to expand the pharmacovigilance center of SBDMA to cover the whole country and implement the basic steps for establishing pharmacovigilance nationwide. Because the public is not fully aware of the risks of medicines and the possibility of their misuse and abuse, the government of Yemen has decided to dispense drugs only by prescriptions except some medicines which can be dispensed without prescriptions namely over-the-counter (OTC) medicines. However, The MOPHP and the Supreme Board of Drugs and Medical Appliances (SPDMA) fail to regulate, control, and monitor the prescriptions. In general, people in Yemen may not have been very well informed about the potential effects of drugs, and dispensing medication without a valid prescription is common in this country.

All medicines including prescribing-only medicines (POM) such as antibiotics, antipsychotics, cardiovascular drugs can be obtained without a prescription from pharmacies. Pharmacies are mostly run by pharmacy technicians and untrained dispensers, in addition to few qualified pharmacists. Thus we cannot expect that the pharmacy staff would know the detailed impact of a drug they sell to customers. It is commonplace in Yemen, that these dispensers are regarded as ‘physicians’ so frequently

they do diagnosis, prescribing and dispensing of medicines for various health complications and diseases, despite their non-existent knowledge and authority. Rational use of medicines aims to improve the use of medicines by health providers, individuals, and communities through rational prescribing, dispensing, and appropriate use of individuals and the community.

2.9. Future Challenges

Having looked into the demographic and the current pharmaceutical states of Yemen, its health system and services, pharmaceutical policies, trade and production, regulations, financing, pharmaceutical product procurement, and distribution, and finally down to the laymen, their knowledge, attitude, and practice, also the poor handling of information and updates, we can predict several future challenges.

First of all, the authorities need to be educated about the importance of updating the policy and information resources on pharmaceutical products that will be sold or are already sold at the counter. This is the greatest challenge to overcome. The second challenge is to reform the pharmacy curriculum taught in the public, private universities, institutes, to educate the community pharmacies, drug store owners, and employers. This is because of the importance of formal and continuing education and to increase awareness, as it is common to dispense any medicine without prescription in Yemen. Also, they have to know that their role is not just dispensing but also to educate the patients and consumers about the drugs they are dispensing.

Another challenge is that the number of physicians has outnumbered the clinical pharmacies in the country. Thus, there is a need

for the MOPHP to build more pharmacies, especially in Yemeni hospitals. As the top people are informed and educated about the importance of pharmacovigilance through several campaigns, workshops, talks, or through reading materials, the public also needs to be informed and made aware of the importance of being treated and diagnosed by qualified physicians, rather than depending on the 'diagnosis' of staff working at the pharmacies.

There is also a challenge in identifying and confiscating counterfeit drugs in Yemen. Therefore, drug policing needs to be made stricter and the MOPHP must prepare a guideline on the types of drugs that are sold in the market. The healthcare professionals and the public must be informed of the existence of these counterfeit drugs and to be able to distinguish between drugs that are 'valid' and drugs counterfeited.

Next, Yemen has to think of ways to address the problem of curbing the number of pharmacies and drug stores operated by unqualified persons. This non-qualification issue has contributed to the fact that pharmacy practice has been undermined in Yemen, both in terms of recognition from the Ministry of Higher Education and in terms of the general perception of the state of the profession in Yemen.

2.10. Conclusions

Despite the progress Yemen has made concerning expanding and improving

its health care system over the past decade, the system remains severely underdeveloped. To improve pharmacy practice in Yemen, many changes are crucial, including updating the pharmacy curriculum taught, implementing standards for pharmacy practice, implementing and/or reinforcing pharmacy legislation and regulations, as well as integrating pharmacists more comprehensively in the health care system as a member of the health care team. Additionally, the quality of the pharmacy workforce needs improvement, and awareness needs to be increased among the public, physicians, other health care professionals, and policymakers about the value of pharmacists as health professionals. Everyone, from the MOPHP, the policymakers, to healthcare professionals, and the community have to be educated about pharmacovigilance, the adverse effect of drugs, and the danger of being exposed to them. This is not an easy task but can help the Government address the different pharmaceutical-related challenges and transform Yemen's health care system.

Chapter Three: The Need for Pharmacovigilance Activities in Yemen

3.1. Introduction

Yemen is an Arab country located in the southern Arabian Peninsula. The Kingdom of Saudi Arabia, Oman, the Red Sea, and the Arabian Sea border it. Yemen has a population of approximately 20 million, with more than 70% live in rural areas. The illiteracy rate is still high at about 55.7%. Yemen is

a low-income country with a per capita Gross Domestic Product (GDP) of USD 659.16 The total expenditure on health is not available at present, but the govern mental contribution is about USD 256 million a year or $13 per capita and represents only 2% of the GDP. In general, the health services (either public or private) mainly focus on major cities; though primary health centers/units and polyclinics are scattered throughout the whole country, including some rural areas. The statistical report (2003-2004) of the MoPH shows a total of 136 general hospitals (93 private), 470 polyclinics (341 private), 626 health centers (115 private), 2185 primary health care units, 380 maternity and child health centers, 1768 private pharmacies and a total of 4799 physicians (329 dentists and 974 specialists). In addition, there are a few non-governmental organizations (NGOs) and foreign medical missions [46].

The local pharmaceutical industry is evolving gradually, covering only around 8% of the total market share. Medicines are imported via private sector agents and cover most of the country’s needs.

There are critical health challenges in Yemen, including the high incidence of both communicable diseases (such as malaria, tuberculosis,

schistosomiasis, sexually transmitted infections, and vaccine-preventable diseases) and noncommunicable diseases (such as cardiovascular diseases, renal problems, cancer, and eye diseases). Also, Yemen exhibits a higher prevalence of lifestyle risk factors (including tobacco use, 'qat' chewing, malnutrition, injuries, and accidents) and lacks the necessary sanitation (especially water sanitation) [47].

3.2. Drug Safety Problems in Yemen

Drug safety issues in Yemen include many serious problems that can have detrimental effects:

3.2.1. Smuggling of Medicines

Studies have confirmed that the proportion of drugs entering Yemeni territory via illegal channels amounts to 60% of all imported medicines. According to SBDMA, a society for consumer protection that monitors the use of 192 fake medicines, 176 different drugs are smuggled into Yemen, 46 of which are fake.15 Medicines of doubtful quality, origin, and expiry date are smuggled into the country through illegal channels and pose a serious threat to public health. Exposed to moisture and light during transport, their quality is also affected. Sometimes these medicines become quite popular and the demand for them increases, as in the case of phenolphthalein laxative tablets, which are illegal in Yemen but continue to be sold [48]

3.2.2. Fake Drugs

Huge amounts of fake drugs flood Yemeni markets and pose serious health threats. Many Yemeni patients have become victims of fake drugs that are not appropriate for human use. Faking of medicines generally begins with the most sought after and rare drug types and then further expanded to other therapeutic categories. Faking of medicines can only be identified by their side effects on the patients. There is no control over these drugs' safety, quality, and effectiveness; SBDMA statistics indicate the presence of 46 different fake drugs on the Yemeni market [48].

3.2.3. Policies of Pharmaceutical Companies in Developing Countries

Harmful drugs are still finding their way to developing countries. Some pharmaceutical companies market their products in developing countries, which are banned in their country of origin. These dangerous drugs generally are sold without any concern for the health of the people, assisted by weak legislation and poor legal control of medicines in these countries. One expert noted that the goal of the multinational companies that have planted their roots in developing countries is to achieve the highest level of profit regardless of humanitarian considerations. Pharmaceutical companies are not alone in using developing countries in this manner; contaminated food and radioactive waste were also shipped to developing countries for disposal [49]. Ten thousand companies produce drugs in the world, but 90% of the drug trade is controlled by 100 companies, of which only 25 multinational companies account for 60% of international sales [50]. Forty-five percent of the poorest nations of the world are still entirely dependent on imported medicines. The third world produces only 10% of all medicines [49].

3.2.4.The Lack of An Active National Drug Policy

The primary goal of any policy is to ensure the availability of safe and effective, and quality medicines to meet the healthcare needs of the country .Drug policy is an integral part of any comprehensive policy for health care. The formation of any national drug policy should take into account the health situation in the country, the medical care system, education and training of health care workers, possibilities for research, and local production of medicines. The demand for medicines, distribution systems, possibilities for the evaluation and control of drugs, and international policies for pharmaceutical products are some of the other factors that should be considered at the time of the formation of National Drug Policy. The need for national drug policy and national system to monitor drug production and the presence of good governance to regulate matters relating to the implementation of drug control are some of the essential components of a robust functioning healthcare system [51].

3.2.5. The Lack of Legislation

To date, no legislation and regulation are governing the distribution and importation of drugs. There are no laws for the selection, registration, marketing, and testing of medicines as well as no checks and balances to control importers and stop smuggling.

3.2.6. The weakness of the Local Industry

The national pharmaceutical industry in Yemen is still emerging. It is still far short of the demand for domestic consumption. The eight existing local factories meet only 8.5% of the actual need in Yemen. They are unable to compete with world-famous brand names, and some of their products have lost credibility with Yemeni consumers. Also, the local companies manufacture only medicines that will result in a quick profit and are even unable to manufacture some life-saving drugs, worth mentioning are the therapeutic categories related to tuberculosis and cancer.

3.2.7. Registration of Medicines Without Scientific Criteria

The process of evaluation and registration of drugs should be based on the established requirements of quality, safety, efficacy, necessity, and cost of drugs. The standards applied to the selection of the drugs should meet the following parameters:

1. Drugs must be selected based on scientific documentation.
2. The ratio between toxicity and effectiveness of a drug must be balanced by the severity of the disease.
3. The benefits of new drugs must be weighed against the availability of better therapeutic drugs in the market.
4. Combinations of drugs must be avoided unless and until it is clear that the compound has the advantages of both constituent drugs.
5. The definite medical need for new drug products should exist, and there should be the medical justification of this need.
6. Drugs must be approved for a specific term (e.g., five years).

7. The price of drugs should be acceptable.

8. Importation of unnecessary medicines

The private sector benefits from importing unsafe, nonessential, and unnecessary medicines, merchandised by different means. World Bank study indicated that 41% of medicines imported in Yemen are unnecessary [48]. The importation of such medicines from abroad exacerbates Yemen's imbalance in payments. Yemen officially imports 13,000 products that cost around 50 million Yemeni Riyals every year [51].

3.2.8. Uncontrolled Medicine Distribution

Planned medicine distribution aims to meet public health needs. Distribution of medicines through agents and pharmacies should take into consideration the population density, the distance, and transport requirements.

Governmental medicines generally distribute via central stores to government clinics without the consideration of real need. The conditions in which these drugs are stored leave them susceptible to the sun, the rain, and theft. There is no control over the private sector, which distributes medicines through pharmacies far more efficiently than public-sector distribution. The private sector nurtures financial gains and sometimes distributes dangerous medicines.

3.2.9. Improper Prescription of Drugs by Physicians

Some physicians prescribe medicines to patients unnecessarily. Others prescribe the wrong medicine or one that is not consistent with the diagnosis. At other times, unsafe medicines are being prescribed for minor cases; either in response to the patient's desire or because the physician believes that more intensive treatment is better. Some physicians even prescribe medicines without a diagnosis when their clinics are crowded.

3.2.10. Improper Dispensing by Pharmacists or Salespeople

Some pharmacists dispense drugs incorrectly. They aim to sell medicines for profit without adherence to the basic standards of humanity and ethics of the profession of pharmacy. For example, they may switch the medicine prescribed by a physician with a similar drug available in the pharmacy. The pharmacist does not explain the indications, contradictions, or side effects of the drug to the patient. Pharmacists sell prescription drugs, including sedatives and antibiotics, without a prescription. Many workers in the pharmacies do not have a higher education.

They often lack adequate scientific understanding, and some of them know only the names and locations of the medicines on the shelves of the pharmacy.

3.2.11. Improper Consumption

The increased demand for and widespread use of drugs (13,000 drugs are already registered) are very serious problems in Yemen. The widening network of drug distribution, pharmacies, and wholesale distributors and the increasing number of smuggled drugs add to the problem. Yemen imports medicines from 117 companies from 54 different countries [52]. All of this has led to a pharmaceutical consumption crisis with the following adverse consequences: First, the irrational use of medicines, improper self-medication, or the overuse of medicines prescribed by doctors as some doctors prescribe more than seven medicines in one prescription. Secondly, the adverse effects of these drugs are a major concern. The government is unable to test the quality and efficacy of these drugs due to the huge quantity of medicines coming from labs where the production of these medicines was not appropriately monitored. Also, some doctors fail to prescribe proper medicines due to the marketing of one drug under multiple names and confusion over the overlapping benefits of multiple medications.

3.2.12. Improper Use of Medicines By Patients

The majority of patients do not follow the treatment prescribed by their doctors. Around 50% of patients do not properly use their medicines. The patients' level of commitment to treatment decreases with time or after the disappearance of symptoms. In addition, sometimes the patient cannot buy the full course or the real medication prescribed, but they buy other medicines in the prescription, intending to treat the symptoms of the disease rather than the disease itself. The high illiteracy rate of the Yemeni population makes it impossible for most people to read the instructions that come with their medicines. Thus, there is no awareness about indications, contradictions, side effects, and expiry date.

3.2.13. Improper Self-Medication

Some patients treat themselves or their relatives without consulting a medical doctor. This can lead to adverse consequences for the health of Yemen's citizens as those who self-medicate are likely to be unaware of how to do so properly.

3.2.14. Lack of Quality Monitoring After Marketing

Yemeni medical authorities do not monitor the quality of medicines after marketing. Many ineffective drugs of poor quality are available in the market. Improper storage in most pharmacies can be detrimental to drug quality and effectiveness.

3.2.15. Lack of Monitoring of ADRs

Monitoring and control of the harmful effects of drugs are one of the key components of any national drug policy. The prerequisites for monitoring of ADRs are:

- Measures to obtain information on medicines.
- Development of measures to take appropriate action on medicines causing adverse reactions in a timely manner.

First, doctors and pharmacists should report ADRs and notify health authorities and stakeholders. When a severe ADR is reported, scientific studies are advised to be conducted by medical and pharmacological researchers. Second, several measures can be taken following notification of an ADR:

- Withdrawal of the drug from the market.
- Banning of selling and importing.
- Cancellation of registration.Destruction of existing stocks of the drug.Warning doctors, pharmacists, and consumers.

3.2.16. Unethical Promotion of Medicines

Unethical promotion of medicines is the norm of pharmaceutical companies. The representatives of these companies do not explain the risks that may arise from the use of their medications. Some companies promote their drugs only by distributing gifts and samples and thus create a real demand for ineffective or harmful medicines.

3.2.17. No oversight of Medical Prescriptions

A medical prescription is a legal document and must have accurate information, transparent with the seal of the physician, including his/her name, telephone number, and license number. Doctors should be encouraged to write prescriptions using generic names.

3.2.18. Medical Errors

The incidence of medical errors has increased in Yemeni hospitals due to ignorance or the incompetence of the medical staff. Many patients suffered due to medical and prescription errors, leading to morbidity and mortality. One must recognize that some complications that occur in the course of treatment cannot be avoided or predicted. The majority of medical errors do not result in legal action, and there is no strict oversight of the work of doctors and nurses by the medical authorities.

3.2.19. Conclusion

Yemen facing many medicine-related problems. Therefore, it is necessary to implement strategies to ensure patients and public safety concerning medicines use. In developing countries generally, there is limited coverage and under-reporting of ADRs. In Yemen, despite the presence of a pharmacovigilance center, there is no published information about its work and no reports. The effectiveness of pharmacovigilance activities in a country is directly dependent on the active participation of health professionals, patients, and consumers. The more information about ADRs collected will definitely be useful for creating a national database. Therefore all should be briefed regarding the ADRs reporting system and encouraged to report ADRs even suspected ones.

Once this proposal succeeds, a plan of action should be developed to establish similar centers to extend the services to other governorates in Yemen

Chapter Four: Current Pharmacovigilance Program in Yemen

4.1. Introduction

At present, the monitoring of adverse drug reactions was launched in Yemen by establishing a pharmacovigilance center in 2011. Currently, there is no published information about its activities, number of reports, and how they process reported documents. The country and public are encountered with many safety problems related to drug smuggling, counterfeit drugs, improper and irrational use of drugs, importation of unnecessary drugs, and medical errors. Therefore, it is necessary to take serious steps and clear regulations in Yemen to ensure patients and public safety concerning medicines use.

Academics from the Faculty of Pharmacy in Aden University decided recently accompanied with appointed representatives of SBDMA in Aden to initiate a pharmacovigilance program in Yemen, to activate the pharmacovigilance center of SBDMA to cover the whole country and to establish a plan to implement the basic steps for the establishing pharmacovigilance program according to Uppsala Monitoring Centre (UMC) Guidelines.

Activities began towards the end of 2014 by reviving the center, designing a website, and reporting forms for health care providers (HCP) and consumers to raise awareness among HCP and consumers.

There were some articles in Yemeni journals that were published as well as many posters were distributed in hospitals to achieve the desired objective. Several educational interventions were conducted among HCP in hospitals and teaching pharmacovigilance for pharmacy students at Aden University and conducting research activities in pharmacovigilance.

Dr.Alshakka (2014) has studied the current practices of pharmacovigilance when he surveyed for CPDs in Aden [53]

He reported poor KAP towards ADR reporting and pharmacovigilance. Participants have insufficient knowledge about pharmacovigilance practices, operation, purpose, and usefulness. The results emphasized the importance of continuing efforts to promote the ADR program to ensure patient and public safety concerning medicine use. Education and training of health professionals and the public will be important in increasing and maintaining ADR reporting. In another paper, Alshakka et al (2015) found a relatively good level of pharmacovigilance knowledge among physicians and nurses. Nurses had had a more positive perception towards pharmacovigilance compared to physicians who more valued consumer reporting [54].

The National Centre follow up drugs after marketing, assess the quality of pharmaceuticals, disclose side effects, and evaluate and develop solutions leading to prevent these incidents, and receive communications on this matter, as well as follow-up news from international bodies and organizations to make appropriate decisions about the safety of pharmaceuticals traded.

4.2. The Objectives of the Yemeni Pharmacovigilance Center

1. Detect, early, of the symptoms of drug side effects.
2. Discover the increased frequency of the known side effects of some medications
3. Identify the risk factors and symptoms of potential mechanical side.
4. Assure quality control of medicines.
5. Prevent damage resulting from the use of medicines.
6. Gather information and opinions regarding the safety of medicines and participating in transparency and clarity in the program.

7. Support and encourage the legalization of the use of medicines to reach the best ways to treat patients and improve public health.
8. Carry education and communication on a global level concerning the safety, efficacy, and quality of pharmaceuticals used in the treatment.

4.3. The Activities of the National Centre

1. Follow-up drugs after marketing.
2. Follow-up reports of the quality of pharmaceuticals and forwards to the relevant departments.
3. Detect side effects, evaluate and develop leading solutions to prevent or reduce their occurrence.
4. Receive communications relating to the safety and quality of medicines.
5. Create a database for dealing with approaching relevant to be used to communicate with them when needed.
6. Follow.-up news from international bodies and organizations.
7 Carry appropriate recommendations about the safety of pharmaceuticals traded, through the decisions of the team pharmacovigilance consultant.
7. Communicate with relevant parties such as agents, pharmaceutical companies, and health professionals to follow up on the implementation of the requirements of the National Centre and to make sure of that.
8. Preparation of annual reports on all activities of the National Centre.
9. Preparation and follow-up training programs to carry out the National Centre for vigilance and medication safety.

Taking into account, the fact that the public is not fully aware of the risks of medicines and the possibility of their misuse and abuse, the government of Yemen has decided to dispense drugs only by prescriptions except for some medicines which can be dispensed without prescriptions

namely OTC medicines. However, The MOPHP and the SPDMA showed incompetence to regulate, control, and monitor the prescriptions. Generally, people in Yemen may not have been very well informed about the potential effects of drugs, and dispensing medication without a valid prescription is common practice in this country. All medicines including POM such as antibiotics, antipsychotics, cardiovascular drugs could be obtained without a prescription from pharmacies. Pharmacies are mostly run by pharmacy technicians and untrained dispensers, probably due to few qualified pharmacists. Thus we cannot expect that the pharmacy staff would comprehend the detailed impact of a drug they are selling to customers. The tragic situation when those dispensers are misinterpreted as 'physicians' for the customers, as they involved many times in diagnosis, prescribing, and dispensing medicines for various health complications and diseases, despite their ill knowledge and against authority rules. This repeated professional misconduct must be rectified. Rational use of medicines aims to improve the use of medicines by health providers, individuals, and communities through rational prescribing, dispensing, and appropriate use of individuals and the community.

Therefore, it is necessary to implement strategies to ensure patients and public safety about medicines use. In developing countries, generally, there is limited coverage and under-reporting of ADRs.

The effectiveness of pharmacovigilance activities in a country is directly dependent on the active participation of health professionals, patients, and consumers. More information about ADRs collected will lead to more useful outcomes as a national database. Therefore all should be briefed regarding the ADRs reporting system and encouraged to report ADRs, even suspected ones.

4.4. Strength and Weakness of The Current Pharmacovigilance Program In Yemen

The strengths of the program are that it is well-linked with the SBDMA.

The major weaknesses of the program are poor awareness among health professionals about pharmacovigilance, the difficulty of a signal generation because unavailability of a national computerized database on the drug prescribed; poor co-ordination to involve pharmaceutical industries on drug safety issues; lack of information generation on genetic effects, and social practices and drug interaction associated with drug use; and also there are only a few reports about traditional and herbal drugs which were widely used.

Another major limitation of the program is underreporting. The reasons for underreporting being uncertainty of types of reaction to report, lack of awareness about the existence, function, and purpose of national ADR reporting. There is also no official reports system for consumers which limits the reporting occurring at the consumer level. Finally, there is no involvement of nursing staff in the ADR monitoring program.

4.5. Program In Yemen

Pharmacovigilance is a modern science concerned with detecting, understanding, evaluating, and preventing the harmful effects of drugs or any other problems related to their use. Pharmacovigilance aim is the safe use of drugs, and this is usually achieved through the spreading of accurate, timely, and relevant information on clinical symptoms. Reporting potential harms to drug use by all physicians, pharmacists, nursing staff and patients is of the utmost priority. It is the responsibility of physicians and health staff in general to report these negative effects of the use of the drug.

Early detection of safety-related signals from clinical trials and post-marketing monitoring and supervision is essential to determine the risks associated with the products. The information gathered during the pre-

marketing phase of drug development may not reveal some rare adverse drug reactions. The drug is used during clinical trials in under controlled conditions, in addition to the limited and selectivity of the number of patients registered in the clinical trials. The use of the drug may not be studied in special circumstances or among a specific population. Hence, monitoring after marketing the drug is extremely important.

The received spontaneous reports on the harmful effects of drugs during the monitoring phase after marketing the drug showed the detection of negative signs resulting from the use of the drug in certain population groups. The Supreme Commission for Medicines and Medical Supplies in our country is making a positive effort in developing the pharmacovigilance program and improving its level by monitoring various reports of the harmful effects of drugs and withdrawing certain types of drugs from the market, and this confirms the importance of focusing attention on the pharmacovigilance approach and increasing it. Concern about improving the current pharmacovigilance infrastructure and highlighting the need to ensure coordination between the systems driving the reporting process for side effects, the continuous monitoring of unwanted effects, and safety aspects of the drugs entering the market.

The strengths of the program are based on the good connection with the High Medicines Authority, which facilitated the procedures, about 27 medicines were withdrawn which described being ineffective and the reports reach to 215 in 2019, which is a good number in the current war conditions, and many educational courses were held in hospitals and some training courses. This is a wonderful achievement in the current conditions of Yemen

The main weaknesses of the program are the weak awareness among health professionals about pharmacovigilance, and difficulty generating signals due to the lack of a national computerized database of prescription drugs, poor coordination of the pharmaceutical industry's involvement on drug safety issues; lack of information generation on genetic effects, social practices and

drug interaction associated with drug use; there are also a few reports of traditional and herbal medicines that have been in common use.

Another major weakness of the program is the lack of reporting. The reasons for underreporting are uncertainty in the types of reporting responsibilities, and a lack of awareness about the existence, function, and purpose of the national vigilance centers. There is also no formal consumer and patient reporting system that limits reporting that takes place at the consumer level. Finally, the nursing staff was not involved in the adverse effects monitoring program.

4.6. Strategies to upgrade the current pharmacovigilance program

Several strategies can be taken to upgrade the current pharmacovigilance program in Yemen. Some of the suggested strategies are listed below:

An awareness program for healthcare professionals

More awareness-raising programs should be conducted regularly for healthcare professionals with an emphasis on the importance and work of the National Pharmacovigilance Program.

Teaching pharmacovigilance

Pharmacovigilance should be taught to the university-related medical, nursing, pharmacy, and other health care curricula to ensure well-prepared graduates in future practice. The pharmacovigilance units should be linked to the (Rational Use of Medicine) RUM center. The Uppsala Monitoring Center (UMC), the international collaborating center for monitoring the adverse effects of medicines, has proposed several essential components of a pharmacovigilance cycle for pharmacologists and other health care professionals.

Patient and consumer notifications:

Strategies must be taken to involve consumers in the Medicines Adverse Reporting Program. Currently, there is very little consumer participation in the pharmacovigilance program.

Educational interventions:

Studies have indicated that continuous visits to doctors, pharmacists, posters, and educational materials such as brochures and leaflets have a profound effect on improving reporting and saving patients from the harmful effects of medicines.

4. 7. Health care Professional Role in Reporting An Adverse Event

As a health professional, you can play an important role in the ongoing safety of medicines and vaccines in Yemen by reporting events to the Yemeni pharmacovigilance center

When you submit a report you contribute to the ongoing collection of information that enables the Yemeni pharmacovigilance center to ensure the safety, effectiveness, and quality of medicines and vaccines.

Why we need your reports

Analysis of adverse event reports is one way that the YPC monitors the safety of therapeutic goods used in Yemen.

There is the potential for an adverse event to occur with the use of any medicine or vaccine - whether it is supplied:

- on prescription
- over-the-counter
- as complementary medicine.

When medicine or vaccine is first registered and made available in Yemen, information about its safety and efficacy is usually available only from clinical trials.

Postmarked monitoring of the safety of medicines and vaccines contributes to a better understanding of their possible adverse effects when they are used outside the controlled conditions of clinical trials.

What actions does the YPC take?

Any information related to the identities of the reporter a the patient will be kept in strict confidence.

All ADR reports are reviewed by a team of professional staff. Serious ADR reports may be reviewed by expert advisors if indicated.

Information of the report will be entered into the ADR database system for analysis

Each adverse event report the YPC receives is entered into a database, which is continually analyzed by YPC staff to identify potential emerging problems for detailed investigation.

If the YPC identifies a safety concern relating to a medicine or vaccine, we can take regulatory action.

This can include:

- disseminating information for consumers and health professionals regarding the problem
- updating the Product Information with new adverse effects, precautions, or warnings
- requiring postmarketing studies
- imposing limits on their use
- investigating manufacturing sites
- recalling products from the market
- suspending or canceling products.

Reports become available on the publicly accessible Database of Adverse Event Notifications.

What you should report

You can report suspected adverse events to any medicine or vaccine available in Yemen, including prescription medicines, over-the-counter medicines, and complementary medicines.

The YPC particularly requests reports of:

- suspected adverse events involving new medicines
- suspected drug interactions
- unexpected adverse events (i.e. reactions that are not described in the Product Information)
- serious adverse events, such as those suspected of causing:
  - inability to work
  - admission to hospital
  - prolongation of hospitalization
  - increased investigation or treatment costs
  - danger to life
  - birth defects
  - death.

Even if you are unsure whether to report, you should report serious adverse events.

What to include in a report

Each report must include:

- contact details for the reporter
- a patient identifier (e.g. initials, but not the full name of the patient or doctor)
- a description of the adverse event
- details of the medicine(s) or vaccine(s) suspected of causing the adverse event.

Please include as many other details as possible.

You don’t need to be certain, just suspicious

You can report any suspected adverse event involving medicine or vaccine, even if you think it might already be known about.

You don’t need to be certain that the medicine or vaccine caused the reaction - a suspicion is enough.

All reports can contribute to YPC’s investigation of a potential problem.

How you can report

You can report:

- online: www.ypvc-sbd.com
- via email: yemenpvcenter@gmail.com

The YPC thanks you for reporting suspected ADRs. These reports are an essential part of ensuring the safety of medicines in Yemen.

4. 8. Conclusion

Though there is a national pharmacovigilance program in Yemen, there are a few limitations with the existing program. The SBDMA in the past has taken several initiatives to promote the concept in the country. Despite these interventions, under-reporting is still a major concern. Strategies need to be taken to improve the ADR reporting culture among various healthcare professionals involved in medication use. pharmacovigilance as science must be embedded in curricula to inculcate proper healthcare practice to students and important to establish a consumer reporting program in the country.

Chapter Five: Teaching Pharmacovigilance for Under Graduated Students: Our Experience at Aden University.

5.1. Introduction

Everybody is exposed to many diseases that necessitate the use of some medicines to treat them. However, using medicine is associated with ADRs that might cause serious health complications. According to studies, almost 5% of all acute hospitalizations were due to ADRs [7, 56, 57].

The rate of hospitalization could be reduced if there is; ADRs monitoring, the realization of the seriousness of the symptoms at the proper time, and adequate knowledge about all aspects of the incidence of these ADRs [7,56]. From here comes the importance of pharmacovigilance (PV) which can be defined as" the science and actions of concerning the recognition, estimation, understanding, and prevention of adverse effects or any other drug-related problem "[3].

To get health professionals with PV competencies, vital aspects of PV should be involved in the educational programs of all health professionals, such as doctors, pharmacists, dentists, and nurses [58].

5.2. Importance of PV for the Pharmacy Students

It can be anticipated that PV teaching at the primary stage of their career, will develop the information about the safety of medicines and skills for a harmless use of medicines [59].

Also, the persistent educational campaign for health workers has proven to be efficient in PV competencies [60].

The pharmacist plays a unique situation to monitor ADRs either by themselves or with the assistance of other health care professionals to

diminish the hazards of ADRs by distinguishing, reporting, and evaluating any proposed ADRs.

They can also educate, recommend, and inspire medical doctors, nurses, and other health care professionals for reporting ADRs.

In Yemen, there is under-reporting of the ADRs due to unawareness of most health care professionals and especially the pharmacists for the reporting process. The under-reporting is an actual problem within PV; definitely, only 6% of all ADRs are assumed to be reported [61].

Though in 2011 the Supreme Board of Drugs and Medical Appliances (SBDMA) launched an official and approved ADRs monitoring system but regrettably, there was no ADRS data reported. In 2014, many activities were carried out such as: starting the center, imitating the website and arranging the reporting form, designing the poster, and procures to start knowledge amongst the athletes, pharmacists, and consumers. In addition, Yemeni magazines have printed numerous articles concerning PV [62].

Unfortunately, the brutal war in 2015 led to complete paralysis in most activities, particularly concerning the monitoring system.

There should be a corporation between the SBDMA and the faculty of pharmacy to restore the activities of ADRs reporting and encouraging the addition of PV to the recent curriculum system as well as the Medicinal alert center should support these activities to ensure a qualified reporting process. Recently, the head of the SBDMA directed an official message to many private and governmental universities urging the need of including the PV as a studying course. He referred that most universities' syllabus worldwide involves a PV course for the importance of this issue. He added, that health workers are the source and developer of the medical alert and safety system so they must have enough knowledge about the reporting of ADRs, managing and observing the cases with the help of the Medical alert center.

The pharmacists reporting ADR awareness is highly influenced by the level of knowledge and attitude for the importance of reporting [63-65]. Some studies showed how reporting could be improved by education and training [66, 67]. Another problem facing Yemen, the pharmacists provide less time in contact with the patients to offer the necessary and required information. The function of pharmacists has been changing from the dispensing of medicine to a more clinical role, and pharmacists in our country have the right to prescribe most medications. For all these problems PV should be taught all health care professionals. The current review focus on the benefit of PV for pharmacy college students.

5.3. (PV) Curriculum for University Education

In spite that the present educational program in the pharmacy faculty in Aden-University includes the essential issue in the ADRs although it is still limited and does not give the students a strong basis, clear and comprehensive knowledge to pharmacovigilance. In many countries in the past 20 years, the university syllabus is based on pharmaceutical chemistry and dispensing. Now approximately 20% of the pharmacy program is dedicated to clinical and about 10% proposed for social and management pharmacy [68,62]. The theoretical aspects of PV are being taught in several developed countries, but the practical issue is absent in third world countries. This might be the stumbling block in establishing a concept. To get a satisfactory outcome in the PV issues, the advantage of the experiences of developed countries in this field should be considered. For instance, the UK attempt to introduce the Yellow card scheme (the system of spontaneous reporting in the UK) into the undergraduate syllabi of medical college which have helped in improving the PV outcomes in hospitals [69], as well as in France a systematic gathering of the ADRs, of approximately 20 years, assisted to graduate a generation of physicians with full knowledge of the risks of side effects and rational use of the drug [70].

The situation differs in developing countries, a study in New Delhi indicated that the knowledge, attitudes, and practices (KAP) concerning ADR monitoring was similar amongst undergraduates and prescribers, but total the scores required development [71].

The suggested curriculum is based on comprehensive outlines and reference books that offer a broad view of all aspects related to the PV. It is recommended to frequently update the information and guidelines. The curriculum should be tailored according to the country's needs because each country has its PV program. There are key aspects stated by the WHO PV principal curriculum for university education that is essential for the anticipated for the acquisition of knowledge or skills outcomes for future health professionals[72].

This WHO PV focus on the clinical aspects of PV in states of only reporting the ADRs since the majority of students will involve in clinical practice and offer patient care facilities. The main intention is to have high competence students in dealing with the PV aspects. The curriculum should increase in complexity by an increase in the academic level. It started with the knowledge of the PV concept and finished with recognizing ADRs, describing the mechanism of ADRs, and be able to recommend pharmacotherapeutic interventions.The curriculum should involve active learning methods instead of passive ones such as; Case studies, solving problems, critical thinking, imitations, application of confident qualified activities, and training at health centers, to have more effective outcomes.PV education can be added to the current courses with limited time investment. Each university should identify the current gaps in their curricula, educate the teaching staff by PV stakeholders, besides that the reporting system for ADRs should be stimulated. It is vastly suggested to have a reporting ADRs system

to provide better prevention and ADRs in health care centers [73]. The value of reports produced rests on the knowledge and training of the clinicians [74].

In 2011 ADRs reporting system was established by the Supreme Board of Drugs and Medical Appliances (SBDMA), though, there is no authorized information or reports released by the SBDMA involving the number of ADRs that occurred and how they processed it. There was a mutual effort between the academics from the Faculty of Pharmacy at the University of Aden and the official SBDMA in this regard [75].

5.4. Objectives of a Pharmacovigilance Teaching Program

There are many important objectives in introducing the PV in the academic curricula of the pharmacy colleges. The main intention is to focus on the patient's situation instead of drug orientation. After completion of the course the student will be able to:

1. Improve patient care and safety about the use of medicines and all medical and paramedical interventions.
2. Improve public health and safety concerning the use of medicines.
3. Detect problems related to the use of medicines and communicate the findings in a timely manner.
4. Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, leading to the prevention of harm and maximization of benefit.
5. Encourage the safe, rational, and more effective (including cost-effective) use of medicines.
6. Promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public.

5.5. Content of the Teaching Program

The content of the current clinical pharmacy syllabus is outlined in Table 1. The teaching outlined to have teaching time10 Hours /Week, divided into Theory (4 hrs./week), Case studies(Theory) (4 hrs./week) and Hospitals (Practical) (2 hrs./week).The course emphasizes the extended role of the pharmacist as patient-oriented rather than drug-oriented. The course is made up of 4 components

1. Clinical Pharmacokinetic: Practical application of pharmacokinetics in Therapeutic drug monitoring and its clinical application
2. Pharmacy practice skills: Acquiring skills to enable the pharmacist to help the public optimizing drug treatment my monitoring and avoiding drug interaction and adverse drug reaction.
3. Pharmacy practice research: An Expertise on the evaluation of medicine through research and utilization reviews
4. Evidence base pharmacy, Evidence base data sources, Answerable clinical questions (PICO) and levels of the evidence base, Evaluation of Medicine and research: Study design, drug information systems, writing a research project

   After completion of the course the student will be able to:

1. Monitor Drug therapy for medication with a narrow therapeutic index and can calculate the most important drug pharmacokinetic parameters

2. Recognize drug interaction due to pharmacokinetic and other mechanisms

3. Respond to question regarding drug information and source evidence base resources for drug information.

4. Conduct a clinical trial and interpret the outcome of clinical data.

5. Predict adverse drug reactions and take action to reduce the events of adverse drug reactions occur.

6. Take patient medical history and admission record

7. Interpret laboratory clinical data

8. To conduct and write research reports.

This syllabus contains some aspects of PV, however, the proposed curriculum based on the WHO PV guideline aims that the student who graduated from the College of Pharmacy must be familiar with the aspects and foundations of PV which can be summarized in the following points: (Table 2).

1. Realizing the value of PV with the pharmacotherapy background.

2. Avoiding the ADRs at the proper time.

3. Identifying the ADRs at the time of occurrence.

4. Proper ADRs management.

5. Reporting ADRs.

The main concern of this outline is to provide the graduate students with the clinical aspects of PV. The students will be in direct contact with the patients so they must have a comprehensive knowledge of the detailed aspects of the PV involving the safety of the prescribed drugs, possible risk factors, the clinical manifestation of the early symptoms of any ADRs reporting the cases…etc. The perspective outcome can only be achieved by involving the PV in the current curriculum of the pharmacy college.

Table 5.1. Content of The Current Clinical Pharmacy Syllabus for Pharmacy Undergraduate At Aden University.

CONTENTS	No. Hours
1.Clinical Pharmacokinetic(PK). a. To provide an introduction to the concepts of clinical pharmacokinetics and therapeutic drug monitoring. b. fundamental parameters, specifically; Volume of Distribution, Clearance, Elimination Rate constant (K), and Half-Life. With examples of the most common drugs. c. pharmacokinetic calculations. d. Pharmacokinetic case studies. e. Pharmacokinetic interaction.	8 Hrs
2. drug interaction (DI). a. Definition & Mechanism. b. Drugs commonly involved in drug interaction. c. Most susceptible people to drug interaction. d. The role of Pharmacist to reduce DI.	3 Hrs
3. Adverse drug reactions (ADR). a. Definition, Types, Mechanism & Epidemiology. b. Predisposing factors. c. Deduction & Reporting.. d. Presentations & Discussions by students. Case report, Cohort studies. Case-control, Spontaneous reporting.	4hrs
4. Clinical Laboratory Data. a. Importance of reference range of biochemical and hematological values. b. Monitoring of blood tests and their reliability. c. Most common disease-induced laboratory values changes. d. Most common drugs and food-induced laboratory values. e. Practical Experiments.	8hrs

CONTENTS	No. Hours
5. Drug information systems. a. Method of gathering and using medical and pharmaceutical information. b. Type of sources for drugs and poisons (primary, Secondary etc.). c. Retrieving, analyzing and evaluating information. d. The use of computer Short course). e. Understanding Clinical trials.	8 Hrs
6. Pharmacogenomics. a. Introduction & Concept.. b. Human drug response c. Polymorphism of Drug metabolism. d. Disease associated polymorphism	3 Hrs
7.Therapeutics. a. Most common CV diseases. b. Most common GI diseases. c. Most common. d. common skin diseases. e. Common Resp. f. Common CNS diseases. g. Common Urological problems. h. Infectious tropical diseases in Yemen.	20 hrs
8. Case studies. a. Heart failure, MI, Angina. b. Hypertension. c. Acute renal Failure. d. Peptic ulcer. e. Epilepsy.	8 hrs
9. Hospital Practice. a. Attend ward round and/or Morning meeting (If available) tropical diseases in Yemen. b. Writing Medical History & understanding the terms and acronyms. c. interpret admission reports and relevance of investigation. d. Study treatment protocols and report on possible contraindication, drug interaction and inappropriate indication.	

Table 5.2. Outline the Main Aspects and Skills That form A PV Core Syllabus for University Education that Is Based on the WHO PV Curriculum.

Main aspect	Knowledge	Skills	Attitude	Examples of teaching methods
Realizing the value of PV	Case-study for a patient admitted to hospital due to serious ADRs	Identifying ADRs and their effect on patients	Broad-Rapy	ADRs historical examples Patient meeting
Avoiding the ADRs	overall hazard factors, Specific hazard factors, Management strategies and protection information	Selecting proper drug therapy	Harmless advising/ dispensing	Problem resolving Imitation of a situation, participate in a role-playing ADR monograph
Identifying the ADRs	ADR categorizing Hazard factors confusing factors Epidemiology	Clinical analysis Causality analysis	Realizing of expected and unexpected ADRs	ADR report evaluation Prescribing safety evaluation training time
Proper ADRs management	ADR categorizing Significance Severity	Select correct activities; patient and HCP communication reporting of ADR data	evaluating hazard-benefit equilibrium in a specific patient	
Reporting ADRs.	Boundaries of premarketing stage Significance of ADR reporting Documentation of ADRs	Distinguishing ADRs in practice Integral reporting form	Obligation for sharing (reporting) of ADRs	ADR reporting task

5.6. Teaching-Learning Evaluation and methods

The teaching methods could be summarized in the following points:

1. Lectures and seminars.
2. Hospital and Primary Health Care Unit (PHC)experiential.
3. Group experimental work.
4. Assignment.

With reverence to contents, the theoretical part can be evaluated using short answer type questions and multiple-choice questions (MCQs). Group activity could be the best way of toassessedADR reporting. The overall evaluation for the course could be carried out by the final written examination. &. Assignment.

5.7. An evaluation of the pharmacovigilance course among students at Aden University

Our team conducted an evaluation of the pharmacovigilance course among our students at Aden University, Faculty of Pharmacy. 50 fifth-year students participated in the survey

The survey tool was developed from a previous literature review about the evaluation of the social courses and modified to meet the objective of the pharmacovigilance course evaluation and translated into Arabic. The content of the English version is attached in appendix 1.

The tool was distributed to 50 students after the PV lecture and give them 15 min to answer the open-ended questions. The data was collected, coded, and running a content analysis because the tool contains open-ended questions.

Most students wanted to know about the types of ADRs and their examples and pictures of the harmful effects. Also, students wanted to know the medication errors in dispensing drugs because they will face all these problems in their future working lives. Some students have a lack of understanding of the causal relation to ADRs and risk assessment and how to fill out reporting forms or know where these forms are available. They preferred to have the multiple-choice questions exam over the direct questions in the exams.

Most of the Students suggested training to fill out reporting forms in seminars, raising awareness and creating day-to-day awareness among health workers and the public, and improving communication with the national PV center

Most students feel the importance of their studies to raise the level of their performance and competence in the future and feel grateful and satisfied with their teachers and that the teaching of the course is very good

5.8. Conclusion

Insertion of the PV in the current academic syllabus is an essential aspect to ensure the safe use of medicines. The suggested curriculum has a hierarchical harmonized structure with a gradual increase in the complexity. The theoretical section is reinforced by practical training. The main aim of applying the curriculum is to have a new generation of pharmacist that have enough knowledge skill in PV and be an active participant in the country PV system.

Appendix-1

An evaluation of your study of pharmacovigilance (PV).

Hopefully, it will take some time to answer the following seven questions and return the completed form to Dr.Alshakka. When giving answers to the questions, you can use the following abbreviations for the components of this course:

a) Lectures;

b) Discussion sessions;

c) Workshop;

d) Assignments;

e) The project;

F) Exam;

G) Textbooks and other educational materials.

1) What are the two most important components that draw your attention to the course on pharmacovigilance? Why?

2) What are the components of the pharmacovigilance course that has less value for your learning? Why?

3) What do you think about the form of the exam and the forms of teaching in general?

4) What is the contribution of the pharmacovigilance course to your professional competence as a future pharmacist?

5) Do you have a message to any specific member (s) of the pharmacovigilance course team, teaching professors, or teaching assistants?

6) Do you have any suggestions on how to make, this course better?

7) What is your comprehensive evaluation of the course?

1.(Excellent)

2. (Very good);

3. (Good)

4. (well)

5. (I don't know)

6. (weak)

7. (bad)

8.(very bad)

Chapter Six: Urgent Need for Monitoring the Safety of Herbal Medicines in Yemen

6.1. Introduction

The medication with traditional herbs is a common practice in different nations for the treatment and prevention of diseases or even for maintenance of health and well-being. Despite the prevalence of this phenomenon in Yemen, there is neither proper regulation that controls the production, standardization, quality control and use nor an appropriate system for herbal pharmacovigilance in Yemen. Yemenis prefer to use herbs before resorting to the use of medicines, sometimes in concomitant or as an alternative to the allopathic medication. Most people have a common belief that herbs are safe, though, there are many side-effects associated with the use of herbal medicines. For the safe and effective use of traditional herbal medication, there should be a regulation from the official authorities, that controls their preparation, selling, quality control, production, and monitoring of the side-effects. The World Health Organization (WHO), stated a guideline for monitoring of herbal safety within the current pharmacovigilance outline. However, monitoring and reporting the adverse effect of allopathic medicines are limited in Yemen and the situation is more complicated and challenging for herbal medicines. The present article summarized the challenges and recommendations for the application of effective herbal pharmacovigilance.

6.2. Use of Herb in Yemen

Since ancient times, herbs have been used for the prevention and treatment of several diseases. In recent times the tendency to use herbs as an alternative treatment is increased dramatically worldwide. Herbal medicines (also called as phytomedicines or phytotherapeutic preparations) are "medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations [76]. Traditional herbal medicine is widely spread among different nations for the treatment and prevention of diseases or even for the maintenance of health and well-being [77]. The practice of using medication from natural origin is a prevalent phenomenon in Yemen like most south Asian countries [78-80]. However, in contrast to the industrialized countries, there is neither proper regulation that controls the production, standardization, quality control and use nor an appropriate system for herbal pharmacovigilance in Yemen. Yemen has a diverse climate due to variation in the natural topography which contributes to the diversity of flora, some of them have been used as herbal medicines [81-85]. Herbal medication in Yemen is based on experience passed down through generations with no scientific reference for most practices. The herbs are sold in the 'Attarah' shops (where spices and herbs are sold) or street vendors without any official authority controlling the process. So, poor quality, incorrect, or adulterated herbs that may have fatal toxicity or side-effects are accessible. A study stated that about 65-80% of the developing countries' populations use herbs for treatments of diseases due to poverty and unavailability of the conventional medicines [86]. Yemen is a poor country too with low socioeconomic levels and prevalence of the various types of acute, chronic, and infectious diseases, most public directed toward using herbal medicine due to their lower cost. Yemenis prefer to use herbs before resorting to the use of medicines, sometimes alongside or as an alternative to the allopathic medication. Even though concomitant use may lead to serious side-effect and health problems but most people have a common belief that herbs if not treat the disease will not be harmful.

6.3. Adverse Effects of Herbs

Herbs are rich with a chemical mixture of organic and inorganic origin that may have specific adverse effects. As a result of the scarcity of research on medicinal herbs used in Yemen, there is a paucity documented information on side effects and safety. Many studies reported side-effects, the potential interaction between conventional drugs and herbs [87-91]. The notion is most people's minds about the safety of using herbs is not true. For instance, some toxic effects were reported [92] for the pyrrolizidine alkaloids (senecionine) which are present in Senecio species [93]. Some herbs are not safe in specific patient groups such as; children, elder patients, breast-feeding, pregnant, and patients with chronic diseases. Also, there is a potential interaction between conventional drugs and herbs. The effect of herbs may be serious if the therapeutic index of the conventional drugs is narrow such as warfarin and phenytoin, or alter the pharmacokinetic and pharmacodynamic properties of the conventional drugs. For instance, hypoglycemia may be resulted due to the use of herbs that reduce blood glucose concentrations with hypoglycaemic drugs. Concurrent use of several herbs in herbal mixtures is not free from health problems as well. Use of poor-quality herbs that contain other parts than the intended one, contamination with toxic substances, microorganisms, and pesticides resulted in unexpected and sometimes life-threatening side-effects [94].

6.4. Herbal Pharmacovigilance

The term pharmacovigilance is a come from the Greek word “Pharmaco” which means medicine and the Latin word “Vigilantia” which means vigilance or watchfulness[95] Pharmacovigilance can be defined as science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problem [96]. Herbal medicines like any other medicines have an adverse effect that may vary from mild to severe [97-100].

Pharmacovigilance aims to improve patient care and safety concerning the use of medicines and to assist public health programs by providing consistent, stable information to evaluate the hazard-benefit profile of medicines. Lately, its field has been extended to involve herbals, blood products, traditional and alternative medicine, vaccines, and other health products. For the safe and effective use of traditional herbal medication, there should be a regulation from the official authorities, that controls their preparation, selling, quality control, production, and monitoring of the side-effects. The World Health Organization (WHO), stated a guideline for monitoring of herbal safety within the current pharmacovigilance outline [96]. However, monitoring and reporting the adverse effect of allopathic medicines are limited in most developing countries especially in Yemen and the situation is more complicated and challenging for herbal medicines. At the patient's level; the underreporting of herbal medicines may be due to attribution of side-effect to the conventional medicines not to the herbal medicine especially if taken componentry or refrain from taking the herb without reporting side effects. At the pharmacists’ level; unawareness of the importance of monitoring of herbal medicine side effects may lead to underreporting.

The practice of using herbs for treatment and prevention of diseases is increasing globally under the term of alternative medicine. As it is a common

practice in developing countries, the health authorities should be aware of the suspected toxicity of some herbs on the liver, kidney, heart, CNS, embryo, side-effects, overdose, allergic reaction, tolerance, dependence-addiction, and others. Pharmacovigilance has principal importance in detecting undesirable reactions. The center of pharmacovigilance was established in Yemen in 2011 by the Supreme Board of Drugs and Medical Appliances (SBDMA). The center initiated some activities however, most of them have been postponed due to the civil war and there is no real official reporting of adverse effects of medicines [62]. In addition to imposing official regulation for the circulation of medicinal herbs, there must be a center to monitor their side effects. There are many difficulties encounter the authorities to establish centers to regulate herbal remedies and monitor side effects such as;

1. Lack of funding for herbal related activities.
2. Low concern about the standardization and quality control of the herbal products.
3. Lack of attention to fighting street vendors.
4. Lack of funding and interest in conducting researches that approve the traditional use of herbs and documents of their main active components.
5. Availability of herbal medicines from several sources that are not related to health professionals.
6. The pharmacists have insufficient knowledge to provide information and consultation on herbal medicines.
7. The inability of the physicians to distinguish that the specific side-effect is due to the consumption of herbal medicines.

There are some recommendations to overcome the existing situation for the indiscriminate uses of herbs.

1. The physicians should concern about the history of taking herbal medication while prescribing the drugs, and the pharmacists should be aware before dispensing drugs as well.

2. Health awareness among the local people must be spread via different types of media for the proper use of herbal medicine, their side-effect, and possible potential harms for the concomitant use with the other drugs, herbs, or traditional medicines.

3. All health care centers should have a pharmacovigilance system that concern about reporting and monitoring not only the side-effects of the dugs but also the herbal medication and possible interaction.

4. Besides continuous education programs for the graduated students and professionals, the academic curricula of all healthcare professionals should be strengthened to enrich the basic knowledge concerning the traditional uses of the herbal medication.

5. Subjecting herbal medicine to standardization and quality control tests in the Supreme Board of the drug & medical Appliances.

6. Supporting the clinical and phytotherapeutics researches concerning the traditional herbal medication.

7. Collaboration between physicians and traditional practitioners is required to provide full case details.

8. Encouraging pharmacoepidemiological study designs to evaluate the safety of herbal medicines.

9. Statutory organizing the sale and circulation of medicinal herbs. Herbal medicines should be prescribed by physicians, pharmacists, or certified herbal practitioners.

10. There should be communication between the local health authorities with the national pharmacovigilance centers to develop proper guidelines for the reporting system.

11. Encouraging herbal medicines side-effects reporting from health-care professionals and consumers.

12. Developing reporting forms either electronic or printed that are combinable with conventional medicines and distributing them to the healthcare centers.

13. Incorporating the concept of the herbal medication and reporting of their side-effects to the medical and health science collages curriculum.

14. Encouraging continuous education campaigns and training for pharmacists and health professionals to increase the awareness about the reporting of side-effects of conventional and herbal medicines.

6.5. Conclusion

It is imperative to increase the health awareness of individuals about traditional herbal medication because they may have a potentially negative effect on public health and insisting in monitor their side effects. The existing center of pharmacovigilance should expand the reporting and monitoring that involve both conventional and herbal medicines. To prevent a recurrence of the thalidomide tragedy in herbal medicines, the local authorities in Yemen must develop a strategy to implement the herbal pharmacovigilance project. There should be close communication with the WHO pharmacovigilance program center for the proper implementation of the nation's pharmacovigilance center.

Chapter Seven: Role of Non-Governmental Organizations in Health and Drug Safety

7.1. Introduction

NGOs have been defined by the World Bank as 'private organizations that pursue activities to relieve suffering, promote the interests of the poor, protect the environment, provide basic social services, or undertake community development. [101]' NGO activities can be local, national, or international [repetition of the information. I think this line should be deleted]. NGOs have contributed to the development of communities around the world and are important partners of many governments - while remaining independent from them. According to the Human Development Report, there were over 37,000 NGOs in the world in 2002, a growth of 19.3% from 1990. Their purposes differ but overall two categories dominate economic development and infrastructure (26%) and research (23%). The involvement of civil society has profoundly affected not only the concepts underpinning public health but the formulation and implantation of public health programs and policies as well. Non-governmental organizations and other civil society actors have engaged themselves to implement health programs at the country level, especially in remote areas and populations, and advocated public health issues to a broad audience. Where drug policies are concerned, most NGOs saw the pressing need to clarify several issues that dwell into essential drugs in NGO work. They have laid the foundation according to several objectives:

i) To ensure that internationally agreed standards of drug policies are translated well into suitable terms for these independent bodies

ii) To introduce, and highlight drug policy components that ascertain a sustainable supply of safe and effective drugs and their proper use

iii) To motivate regular review of policy

iv) To bring into light some emerging issues and conflicts which the NGOs have had to face in this area.

v) To provide information on organizations, networks, training opportunities, and documentation work to advocate development and implementation

The growing role of these organizations and their increasing importance at various levels has meant that they become the voice of the people and their needs and choices and advocate for their rights. They have an important and complementary role in linking and formation of networks and continue to play a useful role in the implementation of policies. They also can communicate with decision-makers and with the media to support and implement these policies. In addition, they can influence people's views. Moreover, these organizations can access large segments of the people and space capacity without bureaucracy and without corruption and take cultural and social initiatives that cannot be easily done by governments.

Why NGOs should be interested in the safe use of Medicines?

Essential drug policies have been outlined by NGOs, based on the WHO essential drugs list and concept, and on top of it, to answer for WHO's long-standing efforts of advising countries to base their drug policies on essential drug concepts. It helps to make sure that scarce resources are well-spent.

Also, medicines have a big impact on people's health and can cause adverse effects which can lead to morbidity and mortality. They also have an impact directly or indirectly on the economic and social affairs. Every medication is potentially hazardous. Therefore, safe and effective drug therapy demands a profound knowledge of every drug product being prescribed, through patient analysis, and adequate patient education. If these three essentials are observed, most drug-induced diseases and most drug-related malpractice litigations can perhaps be avoided. Similarly, costs of inefficient drug management are high, while the benefits (as in better and more cost-effective treatment) can be considerable. Due to this, if more NGOs decide to implement the essential drugs concept, it would be easier to organize and hold joint services, as undertaken by developing countries like Kenya, Nigeria, and India. Linking together internationally also enables the NGOs to compile information and influence policies affecting the welfare of the people they serve.

To get a high level of health is one of the basic human rights that have been declared in the Alma Ata Declaration. This not only means that health facilities must be available to all but also means to enable people to participate, get equal access to health services and ensure their participation in issues that affect their health and their participation in the formulation of policies that affect their lives. Therefore, NGOs can have a major role in pharmaceutical policy. The rational use and safety of medicines are of great value because they represent large segments of the population and their interests. It is necessary to protect consumers and raise the degree of vigilance about the adverse effects of medicines. The urgent need is to access to information for everyone interested in the safety of medicines. NGOs as well as doctors, pharmacists, manufacturers, regulators, the media, and consumers are important players in this area. Therefore, there must be full coordination between the active players with full transparency.

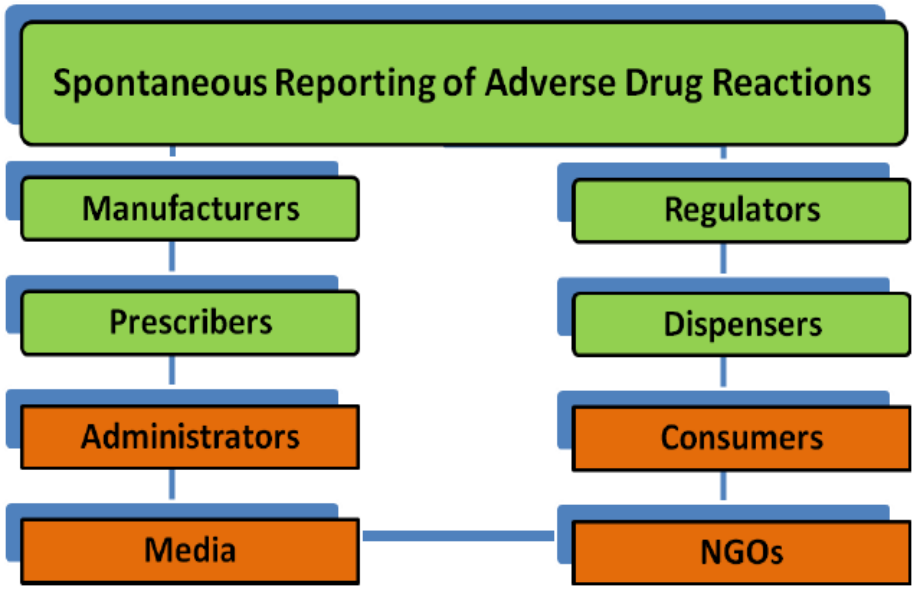

Figure 7.1. Active players in the safe use of medicines.

What needs to be done by the NGOs for ensuring the safe use of medicines?

To ensure better contribution towards the safety of medicines, the following requirements should be fulfilled by the NGOs:

• They should have an active role in the formulation of laws related to pharmaceutical policy and the safety of medicines and ways to avoid the dangers.

• They should have a controlling and observing role that must complement that of government agencies on the safety of medicines.

• They should have the role of education, and awareness on the rational, safe use of medicines and impart basic health knowledge to ensure the proper use of medicines.

• They should protect certain categories of vulnerable consumers, such as the elderly, children, and women from the dangers of certain drugs.

• They have to report and create awareness on the harmful effects of drugs and the importance of monitoring and reporting of fake medicines, unsafe or questionable, or damaged medicines.

• They should educate consumers about the dangerous effects of certain drugs and when the particular drug is withdrawn from the market to stop the circulation of these drugs.

All consumer complaints should be in coordination with the pharmacovigilance centers and other authorized agencies. NGOs can be good channels to express public concerns and problems as a result of the use of dangerous life-threatening drugs.

7.2.The Need for Involvement of Ngos in Drug Safety Issues in Developing Countries

Usually, the involvement of other bodies than the government and its offices in certain national issues is indicative of the fact that the issues are an increasing cause for concern, due to the devastation they incur; such is the case with the HIV/AIDS pandemic that draws everyone's attention to the lack of access to medicines in resource-constrained areas in Africa. In reality, very few developing countries are blessed with structures, systems, or resources needed to support medicine safety activities, and many others lack the unbiased, evidence-based information to help the government make the right treatment decisions and promote rational and effective use of medicines.

There is indeed growing awareness of the extent of safety that the drugs we use every day as remedies and cure for our diseases or illnesses may offer. Where one reaction is mistakenly held as "a coincidence" or NOT a reaction at all, delivery of knowledge over what ADR (adverse drug reaction) constitutes, and the actual experiences one may have, may alert them to the fact that ADR is a serious health issue. This is when the NGO comes into play. As aforementioned, NGOs are closer to the public and becomes the public's "voice" and "channel" for any complications they have emerging from the drug use to reach the government and further, the relevant policymakers. Apart from communicating to the government about the reactions, and informing the mass about the right government channel for reporting ADRs, NGOs are regarded as WHO as working well in areas like distribution and dispensing. A study has found that in developing countries; people's attitudes towards NGOs are more positive when a program is collaborating with various NGOs informally, rather than collaborating with NGOs who are in official connection with WHO. This is despite claims that this lacks sustainability due to the nature of the connection of WHO and NGOs based on personal contacts and the absence of an officer addressing

NGO work in most programs organized. Issues like information gained from the international level that does not reach down to the national level, as found in developing countries like Kenya, Malawi, and Uganda also cannot be taken lightly. For NGOs to properly cater to the public, these independent bodies need to be reminded of several substantial aspects:

a) What are the drugs requested and for whom?

b) Whether the people's needs for certain drugs are assessed?

c) Whether the requests match national or local essential drug lists?

d) The nature of drugs (generic or otherwise)

e) Ways and means for the donor or recipient of drugs to assure the drug quality

And some other related questions and considerations.

An urgent need in developing countries is to get NGOs involved in the safety of medicines because of the following reasons:

• Lack of awareness of drugs and their harmful effects among the health workers and consumers.

• Existence of a program to monitor the safety of medicines in some developing countries through spontaneous reports received from doctors and pharmacists, but the absence of any official channels for the consumers to express their experiences.

• Problem of under-reporting for adverse drug reactions which can hinder the availability of sufficient information on the harmful effects of drugs [102].

• The increasing overuse of medicines without the supervision of medical doctors.

• Less number of reports received by the national pharmacovigilance centers about ADRs in comparison to the countries' population [103].

•The widespread use of herbal and traditional medicines in some developing countries, without the supervision of medical doctors. The unavailability of

sufficient information, people's long-standing belief, and sometimes, superstitions also serve as a barrier to pharmacovigilance or ADR reporting.

• Limited role of NGOs.

• Limited role of mass media in drug safety education.

• Mechanisms to enable NGOs to participate in the safety of medicines.

In line with the problems mentioned above, the researchers suggested the following mechanisms to enable NGOs to participate more strongly in the safety of medicines.

• Better coordination between NGOs, those concerned with the safety of medicines, and the pharmacovigilance centers is needed.

• It is imperative to initiate a program to educate people about pharmacovigilance, its goals, and purpose, and its mechanisms.

• It is recommended to teach and educate people about the harmful effects of medicines and pharmaceutical and medical errors through lectures, pamphlets, and articles in the audio-visual media.

• Consumers, patients, and the media should participate in medicine safety issues and report adverse effects of drugs and a collection of such communications and dissemination of opinions could be useful.

• Strict regulation for counterfeit medicines.

• Framing guidelines for strengthening pharmacovigilance at the policy level.

• NGOs should be encouraged to provide assistance and information about medicines use for the public.

7.3. Role of NGOs in Consumer Reporting of ADRs

Evidence from the Swedish NGO KILEN (Consumer Institute Medicines and Health) shows that KILEN started consumer reporting of ADRs 25 years ago. It was the first step for consumers to be involved in drug safety issues. The consumer reporting started by the NGO in Sweden showed that consumer reporting of ADRs can add more benefits and advantages to the existing spontaneous reporting system. NGOs can play

an important role in detecting, collecting, and analyzing ADRs reports. NGOs can be the best channel for the public to express their suffering and experiences about the harmful effects of their medicines.

The existing system of monitoring ADRs depends on spontaneous reporting by health professionals as the main source of information. Spontaneous reporting is the most widely used method for pharmacovigilance. Despite its inherent limitations, the system provides vital information of clinical importance. The limitations include difficulties with adverse events recognition, underreporting, biases, estimation of population exposure, and report quality [104]. Patients, consumers, and health professionals have the right to be involved to report their experiences and suffering as a result of adverse effects that threaten their health and their lives. The current system of reporting depends on the spontaneous reports written by doctors, pharmacists and when consumers are involved in the process this can reinforce their rights and achieve justice.

The consumer's experiences and views can be used and could provide good tools for information about ADRs [105]. This report increases the amount of knowledge that reveals significant indicators of the damage caused by the medicine.

However, as we talk about developed countries, only a few countries currently accept consumer reports: Sweden (1978), Denmark (2003), Netherlands (2004), USA (1993), Canada (2003), Australia (2003), UK(2005) and New Zealand [106].

The consumer can report directly to medicinal agencies or indirectly through consumer organizations or NGOs. They are also able to submit electronic reports or paper and telephone reports. Experience in the Netherlands obtained during three years showed that patients' reporting

can be a good information source for drug safety monitoring and has qualitative and quantitative value [106].

Blenkinsopp [106] wrote a systematic review of patients' reporting of suspected ADRs. The MHRA team showed more evidence and advantages from international experience regarding patients reporting. They concluded that there is a lack of publication about patients' reporting of ADRs as the number of published studies is very small [107].

A qualitative examination of patients' reports has shown that they were rich in terms of their description of nature, severity, and significance of reactions[108]. Authors from Sri Lanka suggested that consumer reporting is the best method for developing countries to overcome under-reporting and can complement the existing system of reporting based on physicians and pharmacists [109].

7.4. Importance of Consumer Reporting in Developing Countries

Consumers are active players in drug safety and key stakeholders concerning pharmacovigilance and can actively contribute through an integrated and efficient reporting system. Direct reporting is an essential tool to empower consumers and to improve their involvement in the management of their health. With consumer reporting, ADRs will be detected earlier, more ADRs would be reported especially to over the counter medicines. Consumer reporting can be a useful method to overcome under-reporting. Consumer reporting can be a good solution for the limitations of the existing system based on health professional's reports. Consumer reporting will promote consumer rights. Consumer reporting cannot replace the existing system but can complement and strengthen it. Of course, the importance of consumer reporting would not have been known to he public, if 'consumer reporting' is not defined clearly and to exacerbate this, if the public does not know where

to turn to, to lodge their reports. This is perhaps explaining why under-reporting is a major problem, more so in the developing world than their developed counterparts. A different approach is perhaps, needed for pharmacovigilance especially in developing countries, where a lot of basic life aspects like health, education, and living status have put their people at a disadvantaged position, as compared to those in developed countries.

7.5. Conclusion

Various relevant bodies in developing countries should play an important role in detecting, collecting, and analyzing ADRs and other drug-related problems. NGOs should coordinate with regulatory bodies and pharmacovigilance canters in the countries to educate the public regarding drug safety and the harmful effects of medicines. The involvement of NGOs in drug safety activities can add more benefits and advantages to overcome under-reporting, increase knowledge about ADRs, promote consumer rights, and improve patients' safety in these countries. Other than forming coalitions with other world NGOs involved in drug distribution and supply in the pursuit of creating partners for national drug programs and WHO, what is more, important perhaps, is for the NGOs to define and establish their role in drug distribution and supply.

Chapter Eight: Importance of Consumer Evolvement in Reporting ADRs

8.1. Introduction

To Olsson (2001) pharmacovigilance is the science relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems‘[51]The World Health Organization (WHO) defines an ADR as any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose‘ [2].

The WHO reported that ADRs are responsible for a significant number of hospital admissions with reports ranging from 0.3% to 11% of cases [110]. For instance, it has been estimated that over 770,000 people are injured or die each year from adverse drug events[5]. A commonly quoted meta-analysis performed in the United States indicated that ADRs were between the fourth and sixth most common cause of death in 1997 [6].

A few studies have examined the rate of ADRs in developing countries. A prospective observational study from Iran found that 11.8% of patients had experienced at least one ADR [12]. In another study from Iran, approximately 16.8% of patients had had at least one ADR and 2.9% of the ADRs were identified as lethal [13]. Another study from South India reported an overall incidence of 9.8%. This included 3.4% ADR-related admissions and 3.7% of reactions that occurred during the hospital stay[14]. A retrospective study from Riyadh, Saudi Arabia reported that 54% of the ADRs were preventable.

The prevalence per year ranged from 0.07% in 1993 to 0.003% in 1999[112]. In Nepal, the prevalence of ADRs was 0.86%, the male to female ratio was 0.85, and 10.81% of the ADRs were considered severe [15].

It is essential to monitor ADRs to minimize or prevent harm to patients arising from their drugs, to detect ADRs before they are clinically manifested, and to obtain much more knowledge to ensure safe usage of drugs and to assess the harm, benefits, and risks of available drugs [110].

Recently, concerns over ADRs have been widened to include herbal, traditional, and complementary medicines, blood products, biological agents, medical devices, and vaccines [110].

A few other areas are also of relevance to pharmacovigilance, including substandard medicines, medication errors, lack of accurate reports, use of medicines for indications that are not approved and for which there is an inadequate scientific basis, case reports of acute and chronic poisoning, assessment of drug-related mortality, abuse and misuse of medicines, adverse interactions of medicines with chemicals, other medicines, and food.

This topic first appeared on the medical scene 50 years ago. At the time of the thalidomide disaster in the 1960s which resulted in embryonic malformations in thousands of children whose mothers had used the drug during pregnancy, discussion of this topic became highly animated and interest in the safety of medicine emerged.

In the 1960s the WHO began the global monitoring of drugs on an international scale and therefore created the need for pharmacovigilance because the medical information that is gathered before marketing any specific drug is always incomplete. Testing the effects of medicine on animals cannot be used as evidence for human beings, and any tests carried out on the latter involve only small numbers. Therefore, the effects of the medicine can only be assessed properly when the drug is widely used, and differences between countries may occur [110].

8.2. Human Right to The Highest Standard of Health

The right to the highest standard of health is one of the human rights stemming from the Declaration of Alma Ata‘. Health does not mean only that the health system must be available to all according to their needs, and does not depend only on the results of treatment, but also the course of this process, for example, transparency, participation, equality, and fairness[112].

Access to health services and information and the right to the highest attainable standards of health and health information enhance the health of both individuals and communities. A degree of transparency ensures that all key partners including the patients and public and private sectors, international organizations, and civil organizations will receive the correct treatment.

The participation of everyone on issues that affect and have an impact on human health is a right for all and includes participation in defining strategies, development, and policy-making, implementation, and accountability according to the Declaration of Alma Ata. Fairness and equality are among the most basic elements of international human rights [112].

8.3. Need for Local Pharmacovigilance Programs in Every Country

Differences exist between countries (and even regions within countries) in the occurrence of ADRs and other drug-related problems. This may be due to differences in[50]:

- disease.
- prescribing practices.
- genetics.
- diet.
- traditions.
- drug manufacturing processes, which influence pharmaceutical quality and composition.
- drug distribution and use, including indications, dose, and availability.

Besides, the use of traditional and complementary drugs may pose specific toxicological problems, when used alone or in combination with other drugs.

Data derived from within a country or region may have greater relevance and educational value and may encourage national regulatory decision-making. Information obtained in one country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may differ. Therefore, drug monitoring is of tremendous value as a tool for detecting ADRs and specifically concerning counterfeit and substandard quality products. ADR monitoring helps ensure that patients obtain safe and efficacious products.

8.4. Weaknesses of the National Pharmacovigilance Programme in Yemen

The major weaknesses of the program are the lack of awareness among health professionals regarding pharmacovigilance; the difficulty of signal generation, because there is no national computerized database on drug prescriptions; the inability to involve pharmaceutical industries on drug safety issues; the lack of information generated on genetic effects and social practices and drug interactions associated with drug use; and the scarcity of reports about traditional and herbal drugs that are however widely used.

Another major limitation of the program is under-reporting in

Importance of Consumer Reporting

There are several significant reasons for consumer reporting:

1. Consumers are active players in drug safety and key stakeholders concerning pharmacovigilance and can actively contribute through an integrated and efficient reporting system.
2. Direct reporting is an essential tool to empower consumers and to improve their involvement in the management of their health.

3. With consumer reporting, ADRs are detected earlier and therefore, more ADRs are reported e.g. (over-the-counter) medicines.

4. Consumer reporting can be a useful method to overcome under-reporting.

5. Consumer reporting can be a good solution to overcome the limitation of the existing system based on health professionals‘ reports.

6. Consumer reporting will promote consumer rights.

7. Consumer reporting cannot replace the existing system but can complement and strengthen it.

What are the benefits of consumer reporting?

There are several benefits associated with consumer reporting about the adverse effects of medicines:

1. A new source of information for the regulatory bodies of medicines in many countries: Consumer reporting is an important source of new information on the harmful effects of drugs that could benefit the regulatory authorities and is also an important source reports made by patients differed from that of doctors, providing more information on the impact of medicine on the quality of life [106].

2. The reporting of serious adverse effects: The center of pharmacovigilance in The Netherlands noted that reports by patients provide information on serious adverse effects.

3. Different styles, but the same quality: Patients do not use the expressions used by doctors and pharmacists. Therefore, the authorities noted that it is difficult to assess their reports and that this requires more time; however, there is no information about the time taken for analysis of these data. Some authors have reported concerns about the quality of the reports and their credibility. However, the Dutch pharmacovigilance center pointed out that patient reports have the same amount of information as those provided by health workers.

4. Reports by elderly people: A group of Belgian authors compared reports made by 168 elderly patients and those made by their healthcare

providers. The authors asked the patients to explain the reason for their admission to the hospital. The patients reported 33 adverse effects whereas only 12 out of these 33 reports were submitted. The doctors reported serious adverse effects, while the patients reported the effects that made them stay in hospital.

5. Patients report effects that have a strong relationship with drugs: Researchers from the U.S. interviewed 198 patients by telephone and the results of this study indicated that health workers reported only half of the complaints made by the patients.

International experiences on consumer reporting of ADRs of information in clinical practice [106, 113,114].

6. Disclosure of effects that were previously unknown: When consumer reporting began in Denmark in 2003, the first year saw 149 reports from patients, which represented 7% of all reports.

One-third of these consumer reports were unknown adverse reactions.

7. Earlier reporting than from health professionals: a study in The Netherlands suggested that patients recognize and report adverse effects more quickly and earlier than health workers.

8. Increase in the number of reports: In the United States, consumer reporting began in 1993, and in 2004, reports by patients accounted for 15% of the 24,553 reports made in total.

9. Quality of Life: Analysis of data in Sweden by the pharmacovigilance center revealed that the style of.

1. Sweden

The Swedish consumer organization, KILEN, started its activities on consumer reporting since 1978. The experience gained by KILEN showed that the patients can report different things in different ways and some times in far greater volume than do health care professionals. For example between 1984-1988, KILEN received 420 reports about lorazepam, while in the same period, healthcare professionals only report a total of 18. A comparison of 327 consumer reports and 437 physician reports for sertraline showed that there were many side effects reported in greater numbers by consumers [114].

2. The Netherlands

The pharmacovigilance center, LAREB has received reports from consumers since 2003. Besides that, the Dutch Institute for the Proper Use of Medicine (DGV) has run a system for consumer reporting since May 2004. Both systems are linked. Data reported to the DGV are forwarded to LAREB but it can only accept 25% of

ADRs were reported to the DGV. The DGV received 2400 reports in the first 10 months of starting its program. After the first year, LAREB found that reports from patients usually contained sufficient medical information and more frequently referred to serious adverse drug reactions than reports made by health professionals.

3. United Kingdom

The Medicines and Healthcare products Regulatory Agency (MHRA) started a pilot study in 2003. The British yellow card scheme has allowed patients to directly report to the MHRA since January 2005. Patients can submit the report form manually or use electronic reports. Evaluation of the first 6 months of patient reporting using the Yellow Card Scheme in the United Kingdom showed that there were no differences in the proportion of serious ADRs reported, compared with reports made by health professionals.

After one year of consumer online reporting, more than 2,500 yellow cards had been logged by patients or care staff, bringing the total number of patients‘ reports to almost 9,000.

The information collected over one year from online reporting has helped the agency to advise on issues like the adverse psychiatric reaction associated with Rimonabant (Acomplia®) and the withdrawal of its license due to psychiatric risks.

4. Denmark

The Danish Medicines Agency set up a patients‘ reporting system in July 2003, in part as a response to pressure organized by the Danish Consumers Council after it researches an anti-obesity drug. Letigen had shown a greater level of adverse reactions than reporting from professionals alone had indicated, and as in the United Kingdom, attempts to promote to consumers the possibility of reporting were limited; a leaflet produced by the agency was not widely available. Again, as in the United Kingdom, the form that patients can complete is an adaptation that is already used by professionals and employs medical terminology that is not immediately clear to a lay reporter.

5. Belgium

Test-Achats, a member of the European Consumer Association, started an initiative on patient reporting in collaboration with the Belgian Agency of Medicines (FAGG) in November 2006.

The Test-Achats expert team (pharmacists and medical doctors) sends reports to the pharmacovigilance department of the medicines agency. Within a month the agency sends an evaluation back to Test-Achats, which provides feedback to the consumer. From November 2006 to December 2007, 184 ADRs were reported. Test- Achats also registered 56 reports of other drug-related problems and received 31 questions regarding price and reimbursement and 15 regarding the patient information leaflet.

6. Italy

Altroconsumo, a member of the European Consumer Association, launched an initiative known as ―Questa la racconto‖ (―I tell you my story‖) on its web site in June 2006 to collect consumers‘ experiences of adverse reactions following the use of some specific medicines. Initially, they focussed on two creams used to treat eczema, and then they expanded the initiative to coxib and to glitazones used to treat diabetes. In one year, they received 230 reports. The reports were sent to AIFA, the Italian medicines agency.

This initiative showed that consumers‘ reports are essential not only to gather more data about adverse drug reactions but also to determine when medicines are not used appropriately. For example, in the case of the two eczema creams, Altroconsumo showed that they were prescribed for age groups that had not been authorized, as the first option treatment and not as the second option treatment, as required by the competent authorities, and for longer periods than suggested

7. USA

MedWatch, the FDA‘s Safety Information and Adverse Event Reporting Program, offers patients some scope to directly report adverse drug reactions. However, the majority of reports originating from patients that reach the FDA are sent in by the pharmaceutical industry. This sector has a legal obligation to pass on all reports it receives.

Thus, questions and complaints from patients concerning drugs addressed to the marketing authorization holder are categorized as patient reports. A mere 9% of all reports the FDA receives are directly submitted by physicians, pharmacists, or health consumers. Approximately 40% of all reports stem from patients. No studies have examined the contribution of consumer reports to the FDA.

8. Australia

Australia has been taking its first steps towards creating facilities allowing patients to report wrong drug usage since the early 1990s. The Australian Patient Safety Foundation runs and maintains the Australian Incident Monitoring System (AIMS). However, only 20% of the reports concern medication and only 4% of these are about adverse events. The national reporting system (ADRAC) receives about 10,000 reports per year and this includes all appropriately documented patient reports. On an annual basis, the latter comprise fewer than 100 reports.

The need for a consumer reporting program in Yemen. Consumer reporting of ADRs will improve pharmacovigilance in Yemen for the following reasons:

1. The presence of greater amounts of information and awareness will prevent pain and suffering and economic loss in patients.
2. The number of reports made by doctors, pharmacists, and dentists remains low Hence, the consumer will be a rich source of useful information on the harmful effects of drugs and will increase the number of such reports.
3. The existing reporting system has limitations. Worldwide, only a small number (less than 5%) of doctors, pharmacists, and dentists make reports. Several doctors are reluctant to make such reports for fear of legal liability, or the indictment of bad practice.
4. Under-reporting
5. There are a large number of people using traditional drugs without reference to the doctor or failing to

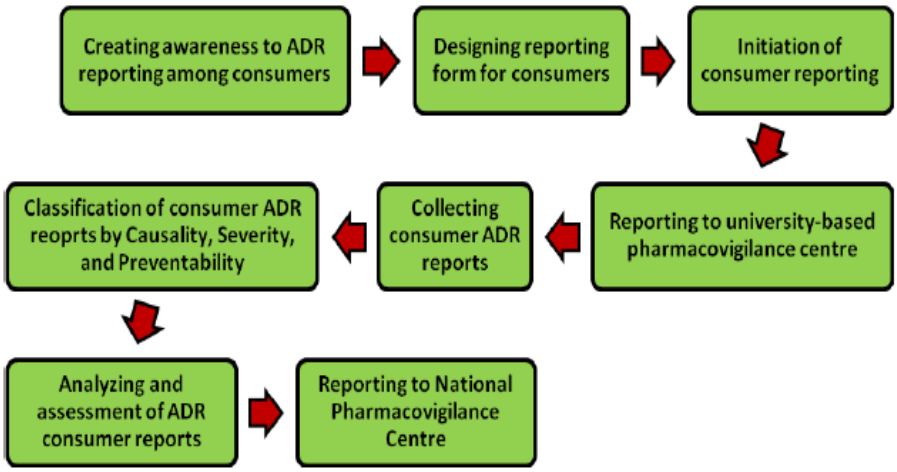

Figure 8.1. An Approach to Initiating A Consumer Reporting Program in Yemen.

8.5. Contribution of Consumer Reporting to Existing Pharmacovigilance Program

Consumer reporting cannot replace the existing pharmacovigilance program but will complement and strengthen it. Consumer reporting has qualitative and quantitative contributions to the existing system. Consumer reporting as a new concept will enhance the impact of the reporting system and improve the knowledge about ADRs stemming from over-the-counter medicine, the off-label use of medications, traditional medicines, and alternative medicines that the doctor may not be familiar with and will therefore not know about their inherent risks.

8.6. Strategies to Improve the Current Pharmacovigilance Program

Several strategies can be used to improve the current pharmacovigilance program in Yemen, some of which are mentioned below:

1. Need to enhance, strengthen, and empower the role of the SBDMA. There is an urgent need to increase the ability of the SBDMA to regulate drugs after marketing and to conduct long-term post-marketing studies for all drugs available in the Yemeni market. The SBDMA also needs to develop active new pharmacoepidemiological methods and tools for its work, train new staff, and increase its resources and funds to improve its work among healthcare professionals and the public.
2. Starting an active awareness program for healthcare professionals to explain the importance, function, and purposes of the national drug safety monitoring program in Yemen. The SBDMA should increase the role of healthcare professionals and the involvement of nursing staff in this program and also in the reporting of ADRs. This will result in increased knowledge about the harmful effects of drugs currently used in the country.
3. Development of a consumer reporting program will provide benefits and advantages to the existing program available in Yemen Hence, it will increase information and knowledge on ADRs, thereby overcoming the main problem of under-reporting and promoting consumer rights. It will eventually improve the quality of life and patient safety in Yemen
4. Strengthening the role and tools of pharmacovigilance science by upgrading new methods for benefits and risk analysis and risk management, thereby strengthening methods and tools for safety surveillance and developing new scientific approaches to detecting, understanding, predicting, and preventing ADRs.
5. Improving communication, information flow, and tools among healthcare professionals as well as the public.
6. Involvement of Non-Governmental Organizations (NGOs) in drug safety issues, given the growing role of NGOs and their importance at the

local level as well as being the global voice of the people. Also, NGOs have expertise and excellent skills in dealing with public interests. They can understand public needs and choices, as well as advocating the rights of the people.

7. The full involvement of drug industries in drug safety issues in Yemen.

8. Inclusion of all providers of local and herbal medicines in the drug safety system in Yemen. The national surveillance program will monitor the system and evaluate ADRs associated with herbal medicine. This is very rare although there is a local elective to communicate on this in rapidly developing and developed countries. There is a lack of methodological uniformity in identification and measurement and a lack of information on ADRs for herbal medicine that is widely used in Yemen and there are very few ADR reports about them in Yemen.

9. Increase the role of mass media in public drug safety education. The media will remain the key provider of drug information and a key player in drug safety issues and can also play an important role in educating the public about the harmful effects of medicines, thus strengthening consumer views about medicines.

10. There is a need for pharmacovigilance subjects to be taught to undergraduate students of medicine, nursing, pharmacy, and other healthcare-related studies. The Uppsala Monitoring Centre (UMC), which is the international collaborating center for ADR monitoring, has suggested many basic components for a pharmacovigilance course and this can be used as a basis for the development of a core curriculum in Yemen for the respective students.

Chapter Nine: Adverse Drug Reactions and Medication Errors: A Quantitative Insight in Aden, Yemen

9.1. Introduction

Pharmacovigilance has not received considerable attention in some developing countries due to a lack of resources and technical expertise. Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems"[50] Pharmacovigilance is an aspect of patient care that seeks to make the best use of drugs and medications for the treatment or prevention of disease without undesired effects. International pharmacovigilance was begun forty years ago to establish an international system of monitoring adverse drug reactions (ADRs), which was a resolution of the twentieth WHO assembly.

Medication errors and adverse drug reactions (ADRs) are of major concern because they result in significant morbidity, mortality, and health care costs. ADRs represent unwanted, uncomfortable, or dangerous effects from a drug [1].

A commonly quoted meta-analysis performed in the United States indicated that ADRs were between the fourth and sixth most common cause of death in 1997[6]. Over 770,000 patients have been injured or died every year due to adverse drug events[112]. and 3.2-7% of acute hospital admissions are solely due to ADRs [4,115]. Furthermore, ADRs increase morbidity, mortality, and the duration of hospital stay, culminating in unwarranted hospital costs[5,116].

The incidence of ADRs has been reported in many studies.

An observational prospective study from Iran identified that 11.75% of patients had experienced at least one ADR [12]. Another study done in Iran reported that approximately 16.8% of patients had at least one ADR and 2.9% of ADRs were identified as lethal [13] A study in South India found that the

overall incidence of ADRs was 9.8%. This included 3.4% of ADR-related hospital admissions and 3.7% of ADRs that occurred during the hospital stay[14]. In Saudi Arabia, a retrospective study showed 54% of ADRs to be preventable. The prevalence per year ranged from 0.07% in 1993 to 0.003% in 1999[111]. In Nepal, the prevalence of ADRs was 0.86% [15].

Also, the male-to-female ratio of patients experiencing ADRs was 0.85 and 10.81% of the ADRs were severe [15].

Safeguards against medication errors are a relevant way to control ADRs. A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm during medication to the patient and is in the control of the health care professional, patient and consumer"[117].

Medication errors may occur at any stage of the medication-use system, including preparation, prescription transcription, dispensation, storage, administration of drugs, and patient and compliance; however, the most common errors take place during prescribing and administration [118].

According to the American Society of Health-System Pharmacist (ASHP) in 2014, medication errors may include "prescribing errors, omission errors, wrong time errors, unauthorized drug errors, wrong.

dosage form errors, improper dose error, wrong drug preparation errors, wrong administration or technique errors, monitoring errors, deteriorated drug errors, compliance errors". Errors arise when an action is intended but not performed; errors that arise from poor planning or inadequate knowledge are characterized as mistakes; those that arise from imperfect execution of well-formulated plans are called slips when an erroneous act is committed and are called lapses when a correct act is omitted [119].

The role of the pharmacist is to provide optimal pharmaceutical care for individual patients and optimal pharmaceutical care is attained when the right drug in the correct dosage and quality reaches the right patients at the right point in time with the right information[120]. In a country at war such as

Yemen, relatively less is known about the extent of medication errors and ADRs and in many health systems, it is not routine to detect them. Pharmacists must be more vigilant, especially in a situation of limited resources during the war.

This study is considered crucial in the present state and it was conducted to estimate the epidemiology of ADRs and medication errors in three hospitals in Aden, Yemen. During the civil conflict, the port city of Aden in the coastal area of Yemen was destroyed. Not only was the political stability affected, but the economic aspects, social services, and health- care system were disrupted, too. The city ran short of food, water, and medical supplies. Such a study in Yemen has not yet been considered; thus, it is beneficial. Specifically, the objectives are as follows:

1. To detect common prescribing and dispensing medication errors.
2. To detect the frequency of adverse drug reactions reporting by healthcare providers (HCP) to the Yemeni Pharmacovigilance Center (YPC) in Aden city.
3. To identify the drugs causing frequent adverse drug reactions.
4. To identify the typical types of adverse drug reactions.

9.2. Methodology

Study Design and Site

To achieve the objective of this research, a cross-sectional prospective study design was used at two different phases of the study. The various ADRs and medication errors reported by HCPs were estimated and analyzed by YPC forms. The study was conducted at Al-Gamhouria Teach- ing-based Hospital, Alsadaqa Hospital, and 22-May-Hospital in Aden city for a period of two months from May to June 2017. Prior permission was obtained from the Ethics Research Committee of the Faculty of Medicine and Health Sciences, Aden University to carry out the study. Informed consent was obtained from all individual participants included in the study.

Ethical Consideration

The Ethics Research Committee of the Faculty of Medicine and Health Sciences, Aden University, had provided ethical clearance for this study. Written informed consent was obtained from all participants who were willing to take part in the study after the objectives, importance, and benefits of the research were described to them.

Study Tools

Two tools were used in this study.

A. Medication errors data collection form: A suitably designed questionnaire was used to analyze the types, frequency, and factors responsible for medication administration errors. Data were collected from the case reports, treatment charts, and medication administration records and by interviewing the in-patients admitted to various wards. Demographic details of the patients and their diagnosis and treatment recommendations were documented. The causes of error due to prescribing and dispensing and the patient's demographic details such as the patient's name, age, sex, address and patient identification number, occupation, allergic history, and social habits were recorded. The prescriber's information included name, date, signature, superscription, and registration number. The information related to the drugs included the name of the drug, strength, drug type (brand/generic), dosage form, quantity, dose, frequency, route of administration, and direction for administration.

B. Adverse drug reaction reporting form: The ADR reporting form is a YPC form of the YPC International College used by health- care professionals. It consists of information related to a patient with an adverse event suspected of being induced by a medication; the form also includes information about the patient, adverse event, suspected medicines or other medicine use including self-medication, the severity of the adverse event, and the name, address and telephone number of the reporter.

Data Collection Method

PHASE 1

All the collected data concerning medication errors were collected, analyzed, and evaluated to determine the types, frequency, and other responsible factors. Analysis parameters were the date of prescription, age, weight, sex, and address of the patient; superscription, name, registration number, and signature of the prescriber; and dosage form, quantity, frequency, and route of administration (May to August 2017).

PHASE 2

A data collection tool for ADRs was designed and reviewed. The face and content validation were done by healthcare experts. All ADR forms were submitted to the YPC unit for further approval. Relevant data were extracted using the data collection tool. ADRs were verified through Mi-Micromedex, Martindale, and the British National Formulary (September 2017) to establish whether the reported adverse reactions were known and documented in the compendia or not.

Participants

Inclusion criteria: All patients admitted to the different wards of the three participating hospitals were included in the study.

Exclusion criteria: Patients treated on an outpatient basis, patients in critical condition requiring a critical care stay, and children under the age of five years were excluded from the study.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) version 19 was the statistical software used to examine, analyze, and evaluate data obtained from study tools. Descriptive statistics were applied to calculate frequency and percentage.

9.3. Results

Phase 1: Detection of Prescribing and Dispensing Medication Errors.

The medication errors were estimated in a total of 265 prescriptions. The results of the study revealed that in all the prescriptions evaluated during this study period, minor and serious medication errors were found.

In the study, the number of male patients was 187 (70.6%) and the number of females was 77 (29.1%). A higher incidence of 174 (65.7%)

Table 9.1. Medication Errors Due to Prescribing (n=265).

S .No.	Parameters	Yes (%)	No (%)
1	Direction mention	38 (14.3)	227 (85.7)
2	Strength mention	56 (21.1)	209 (78.9)
3	Signature mentioned	Nil	265 (100)
4	Reaction with allergy but without allergic speciation	21 (7.9)	244 (92.1)
5	Prescribed two drugs at the same time	52 (19.6)	213 (92.1)
6	Poor handwriting	106 (40)	159 (60)
7	Date absent	57 (21.5)	208 (78.5)
8	Wrong indication	27 (10.2)	238 (89.8)
9	Weight mention	Nil	265 (100)
10	Direction not complete / not legible	4 (1.5)	261 (98.5)
11	Use of abbreviation	30 (11.3)	235 (88.7)
12	Inappropriate use of decimal	252 (95.1)	13 (4.9)
13	Age /Name/Weight	92 (34.7)	173 (65.3)
14	Complete instructions to the patients	17 (6.4)	248 (93.6)
15	Wrong route of administration	15 (5.7)	250 (94.3)
16	Prescribing a drug without informing patients its use and side effect	48 (18.1)	217 (81.9)

Note: The total percentage is not equal to 100% due to missing value.

Table 9.2. Causes of Errors Due to Dispensing.

S. No.	Parameters	Yes (%)	No (%)
1	Dispensing the wrong drug	12 (4.5)	253 (95.5)
2	Dispensing the wrong dose	7 (2.6)	258 (97.4)
3	Inaccurate directions for the use of medication	253 (95.5)	12 (4.5)
4	Failure to educate patient regarding the use of medication	251 (94.7)	14 (5.3)
5	Dispensing an expired medication	3 (1.1)	263 (98.9)
6	Failure to assess, review the patient medication profile	245 (92.5)	20 (7.5%)
7	Dispensing without knowing the patient allergic history	86 (32.5)	179 (67.5)
8	Dispensing g without knowing patient conditions, and medical history (such as why the drug is prescribed)	8 (3)	257 (97)
9	Have a current drug reference available	84 (31.7)	181 (68.3)
10	More than one month of supply given	15 (5.7)	250 (94.3)
11	Substitution/Dispensing product not available	10 (3.8)	255 (96.7)
12	Short supply of medicine	33 (12.5)	232 (87.5)
13	Staff knowledge about medication	13 (4.9)	252 (95.1)
14	Incorrect Label	6 (2.3)	259 (97.7)
15	Short/Expired drug dispensed	15 (5.7)	250 (94.3)
16	Wrong concentration dispensed	7 (2.6)	258 (97.4)

Note: The total percentage is not equal to 100% due to missing value.

Table 9.3. Adverse Drug Reaction and Organ System Involved.

Organ system involved	**N. of ADRs**
Gastrointestinal disorder	72 (32%)
Skin mucous membrane	38 (16.8%)
Respiratory disorder	10 (4.4%)
CNS and neurological disorder	16 (7.1%)
Cardiac disorder	20 (8.9%)
Urinary and Reproductive disorder	12 (5.3%)
Hepato-billiary disorder	6 (2.7%)
Other	51 (22.7%)
Total	225

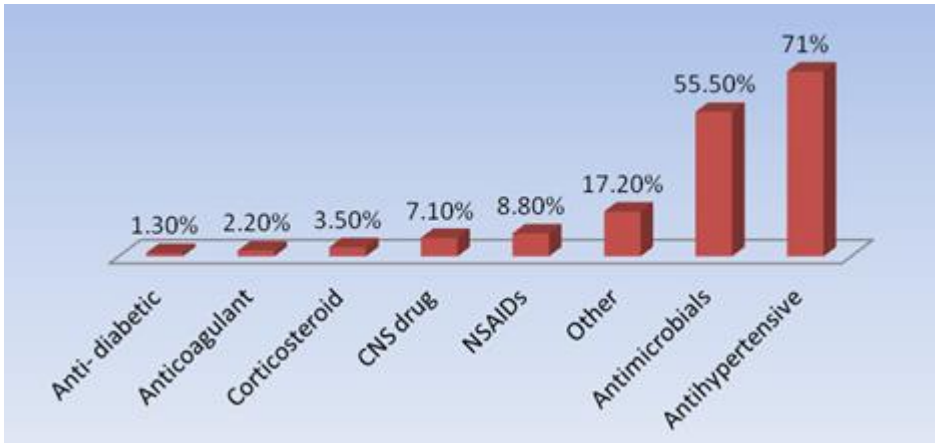

Figure 9.1. Pharmacological Classes of Drug Implicated to Cause Adverse Drug Reaction.

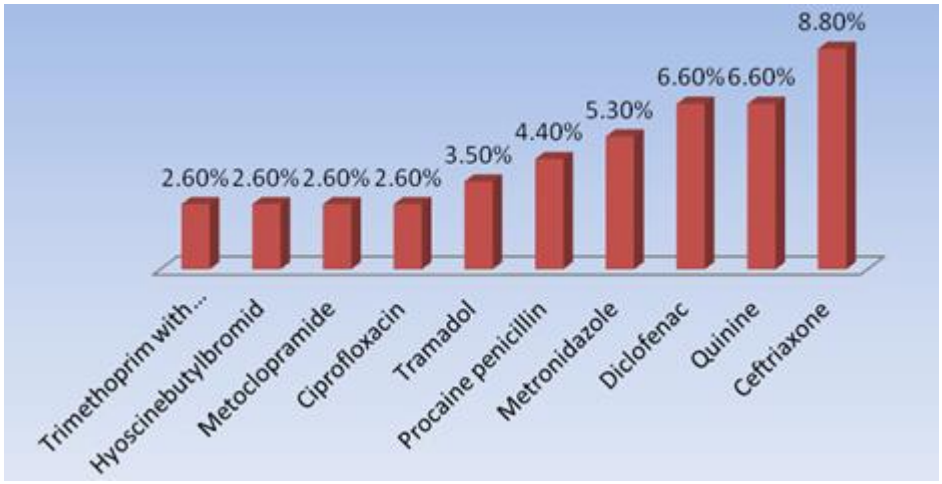

Figure 9.2. Drug Name and No. of Adrs. Report.

Medication errors were found in patients aged less than 35 years, while in patients aged 35 years or more, there were 91 medication errors found (34.3%).

On evaluating the prescribing errors from the collected data on the approved datasheet, it was found that complete instructions to the patients regarding the use and side effects of the drugs were not mentioned in most of the

prescriptions (n=248 (95%)). The highest number of prescribing errors regarded the absence of the weight of the patients (100%) and the registration number of the prescribers (100%). This indicated that while prescribing drugs, the weight of the patient was not considered; the lack of a registration number indicated ambiguity regarding the registered prescriber for prescribing the drugs. Other prescribing errors were inappropriate to the use of decimals (n=252 (95.1%)), which might lead to severe health hazards. Errors concerning the allergic specification on the prescriptions were found in 21 instances (7.9%), which may result in a severe hypersensitivity reaction in the patients if they are allergic to a particular drug. Following this were errors in the use of abbreviations in all the prescriptions studied; this often results in an incorrect interpretation of an abbreviation by the pharmacists or nurses. Abbreviations or acronyms can stand for more than one word and therefore can be misinterpreted. Illegible handwriting in 106 (40%) cases was found to be another important reason for the occurrence of medication errors that may lead to dispensing the wrong drug to the wrong patient (Table 1).

Among various serious errors related to dispensing, the maximum number of errors concerned inaccurate directions (n=253 (95.5%)) for the use of medication and failure to educate patients (n=251 (94.7%)) regarding the use of a medication (Table 2).

Phase 2: Analysis of the ADRs Reported by Healthcare Professionals.

The healthcare professionals reported the ADRs by filling the ADR reporting form. The various ADRs reported by the healthcare professionals and patients were analyzed.

The healthcare professionals reported a total of 225 ADRs. The total number of adverse drug reaction reports over the audit period was 225. ADRs caused by the oral route of administration was the highest, occurring in 166 (73.7%) patients, while ADRs were caused by the oral route of administration only occurring in 2 (0.9%) patients out of 225 patients. More than half of the ADRs reported occurred in male patients (57%) and nearly half (44.24%) of the patients were in the age group of 21-40 years. Among the organ systems

affected, gastrointestinal ADRs constituted a major component followed by skin reactions, as mentioned in Table 3.

There was a spectrum of ADRs reported among the 225 patients. The highest proportion involved skin rashes and allergic reactions and the second highest was nausea and vomiting; other common ADRs were also reported from various drugs used, including gastritis and gastric pain, diarrhea, hypotension, and renal impairment, etc.

The largest number of reports were associated with antihypertensive drugs. Most of the drug categories suspected to cause ADRs were related to antihypertensive drugs, antibiotics and antibacterial drugs NSAIDs, etc.

The anti-diabetic, anticoagulant, corticosteroid, and CNS medications also have roles in ADRs. The drugs other than those in these studies categories play a substantial role in producing ADRs, as mentioned in Figure 1.

Results for the specific drugs related to ADRs showed that ceftriaxone (8.8%) made the highest contribution to ADRs, followed by quinine (6.6%) and diclofenac (6.6%). Generic drugs such as trimethoprim-sulfamethoxazole combination, hyoscinebutybromide, metoclopramide, and ciprofloxacin were found to produce the fewest ADRs (2.6%) as following Figure 2.

9.4. Discussion

Pharmacovigilance plays an indispensable role in inhibiting and overcoming ADR-related problems. Nevertheless, ADR-related monitoring and pharmacovigilance activities are still very minimal in a country such as Yemen, where instances undermining patient drug safety are rampant, as strongly shown in this study. This is a pioneer study in Yemen that evaluates ADR events reported by HCPs. Our objectives were to evaluate data on the issues of pharmacovigilance and ADRs, reporting that can further support the pharmacovigilance system in better ADR reporting and, henceforth, enhance health outcomes as well.

A thorough review of 265 prescriptions indicated serious prescription errors in providing the prescriber signature and the patient’s weight

measurement; other significant errors were inappropriate to use of decimal points, poor handwriting, as well as inconsistencies in writing the age/name of the patient. These prescription errors may result in relevant health hazards to the patient in various manners.

Pharmacist-augmented errors in dispensing further accentuate the contribution to poor outcomes of therapy or the creation of health hazards. Inaccurate directions for use of the medication, failure to educate patients regarding the use of medication, failure to assess and review the patient's medication profile, dispensing without knowing the patient’s his- tory of allergies, and dispensing without having a current drug reference available are major contributory factors. The dispensing errors estimated in this study need to be addressed as soon as possible without any further delay. Benkirane et al. reported that preventable ADEs occurred in the prescribing (71.1%), administration (21.2%), transcription (5.7%), and dispensing stages[121].

According to Gandhi et al. computerized monitoring represents an efficacious approach for identifying ADEs [122].

The ADRs reported by healthcare professionals are also found to be lacking. Out of 225 ADRs, most of them were related to oral administration of medications and caused gastrointestinal disorders. These major ADRs in patients result in suspicions about the rationality of the medication used.

A study conducted in an ICU by Benkirane et al. in 2009 indicated that out of 696 patients studied, approximately 70% of the AEs were considered ADRs [121].

They also mentioned that 53.8% led to potential ADEs and 46.2% led to actual preventable ADEs.

On evaluating the errors by drug class, antihypertensive drugs were found to be the largest contributor of ADRs followed by antibiotics and antibacterial drugs and NSAIDs. This is a serious concern for drug regulatory authorities to address the control of ADRs. On evaluating the ADRs involving generic-name drugs, the study also found that ceftriaxone was the main drug-producing ADRs, followed by quinine and diclofenac. Sakuma et al. reported

that antibiotics were the most frequent cause of ADEs in patients younger than 65 years old[123]. They also mentioned that antihypertensives were most often associated with fatal or life-threatening ADEs (25%) in younger patients.

As we have already estimated that the greatest number of ADRs involved gastrointestinal disorders, the contribution of diclofenac to ADRs is verified. Antibiotics are the most common class of drugs causing ADRs. The irrational use of antibiotics/antibacterials has already been demonstrated by researchers in Yemen [124]. Moreover, in Yemen, community pharmacists dispense antimicrobials without a prescription. Studies from the hospital settings in Yemen have already raised concerns regarding irrational antimicrobial use. Additionally, it is a common problem in both the hospital and community setting that analgesics and NSAIDs are the second most common class of drugs implicated for causing ADRs. NSAID drugs have caused several ADRs, including gastric problems. Many times, they are used OTC by the public. The pharmacist can play an important role in minimizing these ADRs by providing simple information to patients regarding the precautions to be followed while taking these medicines, such as taking them accordingly either before or after food and drinking additional water with the medicine.

A majority of the ADRs were associated with oral administration of medications, followed by the parenteral route. Most of the ADRs with injectable medications were severe. Gastrointestinal-related ADRs were most commonly observed with oral medications. In our study, we found gastrointestinal side effects (e.g., gastritis, dysphagia, etc.) at the top of the list of ADRs followed by skin and subcutaneous disorders. Next, the main groups of side effects noted were related to metabolic, nutritional, CNS, and neurological disorders. Neurological ADRs were at the top of the list of ADRs in previous studies and gastrointestinal ADRs were reported among the top three groups of ADRs [125,126].

The incidence of adverse drug events is directly proportional to the number of drugs being taken and increases remarkably as the number of

drugs rises. Many epidemiological studies of risk factors for adverse drug reactions have shown that the number of concurrently used drugs is the most important predictor of these complications [125-127]. Polyphaser- Macy needs to be discouraged, as a good number of ADRs result from drug-drug interactions[128]. This can be a risk factor in the development of undesirable adverse drug events.

Medication errors can occur anywhere in the healthcare system, from prescriber to dispenser to an administrator and finally to patient use. Thus, the reporting and prevention of medication errors have become an important consideration; the therapeutic outcomes of drug therapy increase with the reduction in the incidence of a medication error, which will ultimately improve the quality of the patient's life.

The major controversy arising from this study is pointing toward the role of both parties, patients, and physicians; usually, the patients are unaware of the ADRs. In our hospital and other health care facilities, documentation of ADRs is unintentionally missed. This could be because of technical issues, a shortage of staff, or a lack of proper sensitization; many times, the mortality and morbidity associated with the ADR are taken as an outcome of the disease processes itself.

Medication errors may be caused by the high number of prescriptions and the limited number of pharmacists. Providing incomplete or simply no drug information to the patient can cause discrepancies between the doctor's prescription and what the patient takes in actual practice. The impact of medication misuse because of these discrepancies can lead to morbidity and mortality. To avoid such medication misuse, pharmacists should provide information and education to the patients until they understand the role of medications in their health.

Our study has its limitations. Underreporting, a well-known limitation of spontaneous reporting programs needs to be taken into consideration while interpreting the data. Since the study data were obtained from only three hospitals, the results may not be generalizable to the entire population.

However, our study data should give insight into the pattern of ADRs that occur in tertiary care hospitals with a comparable pattern of patient demographics and drug usage. In addition, another of our study limitations was the relatively small number of respondents. The target group was chosen conveniently rather than with random sampling. The study findings could not be applied to the whole country because this study was done among the HCP only working in Aden city. It is also worth noting that some of the HCP was not cooperative.

It is worth providing some recommendations to improve the pharmacovigilance activities in countries with poor resources:

1. A course in pharmacovigilance should be incorporated in the pharmacy and medicine curriculum, creating a culture of safety among students in the health care professions.
2. Pharmacovigilance workshops and seminars should be conducted to guide healthcare providers for recognizing and reporting ADRs. Additionally, pharmacovigilance studies should be supported.
3. ADR reporting by healthcare professionals and manufacturing companies as well as by patients and the public should be encouraged.
4. Incentives should be provided to healthcare professionals reporting ADRs not associated with human errors.
5. ADR forms should be collected periodically from health facilities by sending representatives and/or be facilitated by e-mail, fax, and phone.
6. There should be the assurance of non-involvement in legal matters if they arise.

9.5. Conclusion

In summary, the study has assessed the common prescribing and dispensing Medication Errors (MEs), frequency of Adverse Drug Reactions (ADRs), the drugs causing frequent ADRs, and the typical types of ADRs.

It has provided baseline information about the prevalence of ADRs and their distribution regarding different age groups, sexes, affected organ systems, and therapeutic classes of medicines. This study calls for the institution of a 'pharmacovigilance program' and the establishment of pharmacovigilance centers in association with regulatory bodies such as SBDMA (Supreme Board for Drugs and Medical Appliances).

The data presented here will be useful in the development of future, long-term, and more extensive ADR monitoring programs in the hospitals and will be useful in framing policies regarding the rational use of drugs.

9.6. Limitation

Our study has its limitations. Underreporting, a well-known limitation of spontaneous reporting program needs to be taken into consideration while interpreting the data. Since the study data were obtained from only three hospitals, the results may not be generalizable to the entire population. But, our study data would give an insight into the pattern of ADRs which do occur in tertiary care hospitals with a comparable pattern of patient demographics and drug usage. The main limitation of our study was the relatively small number of respondents.

The target group was chosen conveniently rather than random sampling. Another major limitation of our study is that the findings could not be applied to the whole country because this study was done on the HCP working in Aden city only. It is also worth noting that, some of the HCP was not cooperative.

Acknowledgment

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Abbreviations

HCP: Healthcare providers; YPC: Yemeni Pharmacovigilance Center; ADRs: Adverse Drug Reactions; MI: Medication Errors; CNS: Central nervous system; NSAIDs: Non-steroidal anti-inflammatory drugs.

Chapter Ten: Medication Safety Beyond the Hospital and Role of Pharmacists in Ambulatory Medication Safety Process

9.1. Abstract

Medication safety is one of the challenges which is in focus nowadays, and various approaches to reduce the incidence of medication-related problems and risks are ongoing. Most initiatives have concentrated on medication safety in the hospital setting considering the increased risks of medication errors in hospitals. However, there are various factors and areas to be addressed regarding medication safety beyond the hospital setting. Although, attitudes towards medication use are changing among the public and health providers, still the use of medicines beyond hospital settings requires more attention. Great efforts are needed in this area, due to diversity in the types of errors, the relationship between the provider and the patient, information transfer, optimization of e-prescribing systems, the lack of adequate training in analyzing the collected data, and poor practical strategies for maintaining accurate medication lists in electronic medical records. Recently individuals have started becoming aware of the risks of patients' medication exposure, however, still, the area of medication safety beyond the hospital setting needs community pharmacy intervention to avoid malpractice claims and misled decisions in solving medication safety-related problems in the outpatient setting. All these approaches will help in identify and prompt the detection of errors, open productive discussions, quality control checks, and effective wise system based decisions, and subsequently, reduce the harm and risks before a patient is exposed to any form of medication

Keywords: Drug safety, ADRs reporting, Ambulatory care, Role of pharmacists.

9.2. Introduction

It may not be too much of an assumption that the use of medicines can be as complicated as it can ever be. Other than being understood as a form of medical treatment, it is also seen as a way to enhance one's wellbeing and state of health. However, human nature dictates that the medication of various kinds can also be misused for other purposes. Over the years medicine regulation and control have also continued to evolve, and as it is, so have people's views and attitudes toward the use of medicine that medication safety is at stake, be it within the walls of the hospital or pharmacy itself, or one's own home or outside clinical settings. Medicines have been overused, underused, and misused as evident in multiple case studies all over the world [129-133].

9.3. Challenges in Medication Safety Beyond the Hospital

Over the years, not many people have been aware of the risks of medication exposure to patients outside the hospital setting. In America, for instance, the majority of the patient-safety studies and safety-improvement agenda have been carried out within the walls of the clinics or hospitals and statistics has provided evidence that only about 10% of patient-safety studies have been done beyond hospitals[122]. One striking challenge in terms of medication safety beyond the hospital is that there are differences in the types of errors such as treatment errors and diagnostic errors. The treatment errors tend to predominate in inpatient settings, while diagnostic errors are more apparent in outpatient settings [134]. Another challenge lies in the nature of the relationship between the provider and the patient. It appears that adherence is more critical in outpatient settings than the inpatient ones. One also cannot turn a blind eye and a deaf ear to the issue of the organizational structure that also poses a challenge to ensure medication safety beyond the

hospital- it is a fact that ambulatory practices do not have adequate infrastructure and expertise to deal with the quality and safety improvement[136].

Other than that, there are also regulatory and legislative requirements to consider (involving things like the ratio of staff and requirement for accreditation for hospitals; private practices tend to suffer from these problems the most).

To add, the outpatient setting also poses greater challenges for information transfer. Concerning patients with complex medical needs, the responsibility for care is often shared by a lot of different providers. As it is, they never meet, more often than not, and they often use different medical-record systems, suggesting that shortcomings are inevitable. It is not rare that in the hospital if a patient has an adverse drug event, clinicians were fast becoming aware of it; in the outpatient setting, a complication or missed diagnosis may not be identified for months, if ever[122,136].

Perhaps, we cannot overestimate or underestimate the fact that there is still too much to learn about the effects of e-prescribing systems on errors and about how these systems can be optimized. We start by bringing together data on outpatient-safety risks via a better reporting of events and near-misses from the clinicians themselves. Leaders also need to undergo training so that when they receive reports concerning safety, they can dwell on them and start making changes. Provider organizations that have come to be aware of these challenges and respond to them will be the superior ones as the spotlight is increasingly focused on care delivered not just by hospitals but by truly accountable care organizations.

Another challenge is to provide better strategies to maintain the right medication lists in electronic medical records. Many integrated delivery systems, including ours, have to struggle with ‘the nitty-gritty’ like who is responsible for maintaining the accuracy of the medication list. Some

concerns can also be raised if we look at the present systems- if a specialist is the only physician in an organization who attends to the patient, does that specialist have the responsibility to log in all the patient's medications and dosages in the medical record? As the responsible parties work out ways or even resorted to several trial-and-error methods to resolve the issues, clinicians would already have been further overworked[135,136].

Also, missed or delayed diagnoses are the most common problem leading to malpractice claims in the outpatient setting, and practical strategies have been laid out to track and follow up on test results to ensure that results communicated to providers and patients are 100% reliable. Tests revealing findings that are clinically significant but not critical require particular attention. These findings must be communicated appropriately to a responsible provider, where they must acknowledge their receipt, and systems must be put in place to ensure that any follow-up testing would take place and patients are properly informed about this.

Next, important information like follow-up plans and appointments and any other relevant details are sometimes not relayed. A study has shown that almost half of the total number of hospitalized patients have pending test results when they are discharged, and none of the health care authorities are informed about these test results. This failure of transmission suggests that the responsibility is not communicated and maybe distributed well. It is also reasonable to anticipate that discharging hospitals need to implement high-quality discharge summaries that are transmitted reliably, while outpatient physicians' offices need to ensure patient access to timely post-discharge visits where they can go through the discharge materials, reconcile medications, elaborate on symptoms, and perform appropriate follow-up so that the readmission rate can decrease[137].

9.4. Medication Safety in Community Pharmacy

It may be a great help if community pharmacies are equipped with adequate guidelines and manuals or some kind of written guidance on ensuring the safety of the medication used and delivered to patients. One tool that can be used to assist community pharmacies to prepare for the oncoming implementation of a barcode product verification system, helps pharmacy leaders and staff evaluate their current workflow, standard operating procedures, and technology to identify what needs to be accomplished before implementing a barcode product verification system is the Assessing Barcode Verification System Readiness in Community Pharmacies. The assessment process makes the adoption of this technology less stressful and more efficient as the staff have better preparation[138]. Pharmacists and other pharmacy personnel also need to be able to do what they can to ensure the success of the organizations. This includes targeting a specific system's weakness in the medication-use processes. The tasks of community pharmacy personnel include:

1) beginning a risk assessment process to identify system-based medication safety improvements in the community pharmacy setting.

2) identify and prevent risk in daily practice.

3) check on the flow diagrams or flow charts of the medication process to identify the variability in the current medication-use processes.

4) be able to choose effective error reduction strategies that can avert patient harm.

5) apply knowledge to identify breakdowns in the system that have to do with the error, and

6) detect any medication error or near miss that has happened [139]. Next, the ISMP Medication Safety Self-Assessment® for Community/Ambulatory Pharmacy should be actively used by

pharmacists to raise awareness of distinctive characteristics of safe pharmacy systems; this will prepare the basis for pharmacy efforts to improve medication safety and evaluate these efforts[140]. Every layer of the staff within each pharmacy site should be provided with a copy of the assessment and asked to complete the items collectively or individually. There should be a consensus on the responses and doors should be opened for improvement.

The self- assessment should serve as an ongoing safety project in your medication safety program. This monthly innovative newsletter gives vital and potentially life-saving information about medication-related errors, negative drug reactions, as well as recommendations that will help you reduce the risk of medication errors and other adverse drug events in your community practice site[141].

There should also be a confidential national voluntary reporting program that provides expert analysis of the system causes of medication errors and disseminates recommendations for prevention. Of course, we do not want such events to go unreported and to let important preventive and epidemiological information become unavailable. Regulatory agencies and manufacturers should be notified when the products are to be changed to a certain degree. Reporting errors to external reporting programs as an important element would be complementary to the medication safety program and demonstrates a practice's commitment to sharing information on medication errors which may help others as well [142]. Some abbreviations, symbols, and dose designations are also frequently misinterpreted and this can be detrimental to the patients. It is important to realize that these potentially ambiguous and misleading labels are not to be used when giving out and sharing medical information with others [143].

9.5. Medication Safety at Home

Personal care is seemingly the way to go these days, especially in hospitals with too many patients, but the fact remains that many of the people who are cared for in their own homes need help with their medicines. The care provider must be very clear about their care workers-whether care workers are involved in medicine administration or are limited to providing general support for each child or adult they care for. This has to be monitored and reviewed regularly. All in all, the communications between care workers, their supervisors, and prescribers must be robust and effective. Care workers also have to consider a few things - in the case where a person declines on his or her medications[142].

- In the case where a patient experiences a significant change
in his or her mental or physical state
- The ways of communicating between care workers and various parties.

Should a patient be left to handle his or her medication alone, medication safety at home is equally crucial to address. These are some practical steps that can be taken to ensure that medication errors can be avoided.

Suitable or Enough Lighting

As trivial as it may seem, medicines must be prepared in an environment or condition regarded as conducive for that purpose.

As Little Distractions and/or Interruptions As Possible

Interruptions and distractions (including noise) are proven to be two of the leading causes of prescription dispensing and medication errors in hospitals and health systems (45%). It is advisable to turn down the volume of your cell phone, turn off the radio and/or TV and choose a time when you are free and less distracted. Conversing with others while you are trying to dispense medication is also another possible cause for this kind of errors.

Well-organized Workspace or Storing Area

Errors in dispensing medicine can occur too when medications were not properly stored, so proper organization is very important.

Important information should be within reach, frequently used items should also be within reach. Sorting the Items Together Items that are related to a medical procedure should be stored together in a single bin. Follow the Medication Closely – Most medicines should be stored safely in a cool dry place well away from moisture. Nevertheless, some medications require special storage conditions so always adhere to the storage directions contained on the medicine label or the Medication Guide[144].

Have Easy to Follow Prescription Labels

If either the patient or the healthcare professional cannot read or cannot comprehend the label, your pharmacist can help. One way how the difficulty can be reduced is by having the prescriptions written in large fonts. Also, for non-native speakers, the prescription can be written in the patient's native language or the language most familiar to him or her. Another way is to include the information on 'the purpose of use' on the label of the medicine so medication errors can be avoided and adherence further ensured. Next, important documents like the Patient information leaflets should be accessible to patients and the people close to them. Physicians and pharmacists can also take the initiative to create a system that works for the patient and promotes adherence, for instance. Think of a better way for them to record their medication method and procedure.

Tech-savvy patients and healthcare professionals can make use of the apps that concentrate on helping patients with their medication[143].

9.6. Role of Pharmacists in The Ambulatory Medication Safety Process

It is easy to understand that pharmacists should ensure that medicines are delivered to patients safely and securely. Upon dispensing, pharmacists are expected to reconcile prescriptions of the medicine and confirm the indications of medical therapy with the patient or agent. They should also be able to perform counseling and refuse documents that are irrelevant to their patients' cases. They should be able to ask questions to evaluate patient and caregiver level of understanding. Last but not least, before dispensing the medicine, they must be able to motivate their patients and caregivers by way of asking questions or raising concerns about their medicines. Before any of these can be materialized, it is perhaps not too much to urge for pharmacists – locally and internationally- to have an in-depth understanding and genuine awareness of what is at stake if this safety process is neglected.

In short, medication safety leaders must collaborate with all types of health care professionals, support staff, and management and consider all components of the medication-use process in both inpatient and clinic settings to ensure that medication safety can be improved. The medication safety leader's role includes demonstrating the responsibility for leadership, influencing practice change, and various others.

9.7. Recommendations for Improving Medication Safety Beyond the Hospital

Some recommendations are then considered imminent: first of all, pharmacies are to monitor regularly the medications works or studies on drug error information and take action for prevention. Secondly, pharmacies need to be accountable in confirming the entry for new prescription data. They also have to keep going through the error frequencies and near-misses so unfortunate incidents can be prevented and corrections can be made. They must always be ready to report errors to external reporting programs[144].

Next, as a further recommendation, pharmacists should be able to verify patients' identities, other than educating consumers about preventing errors. An equally important task for pharmacies is for them to be able to work on approaches or methods that can monitor prescription-filling machines to prevent errors. Follow-ups must also be done to see if patients have any side-effects especially as far as high-risk patients are concerned.

If we are to focus on a pharmacy and a patient under his or her care, there are several things that the former should do. Firstly, the pharmacist needs to review the patient's medication list routinely. He or she has to go through all the treatment options that the patient can undertake. The name and the purpose of the selected medication then have to be noted. A pharmacist should also be able to open himself to herself to discussions- discussions like when and how to take medications are not only appropriate but also crucial[145].

9.8. Conclusion

The sole reason why medication management takes a very important position in the world of healthcare is that it is supposed to protect patients from harm or ill effects. We have been able to conclude that even though all healthcare practitioners have a role in preventing adverse drug events (ADEs), most medication treatments begin in the (proper) practice setting of physicians and this is further continued to be emphasized at home. Adverse events happen for multifarious reasons. Some of the most common contributing factors at home are the confusion about the medication schedules, two caregivers duplicating a dose and caregivers using the wrong syringe size, or mixing up two different medications.

Factors like language barriers, financial barriers to medication refills, and transitioning patients between multiple households can also impact the safe administration of medications at home. These are the very few cases that have been reported. Medication management is indeed, a collaborative effort coming from physicians, pharmacists, nurses, and other health care professionals together with patients and lay caregivers pursuing optimum and safe use of medication. Medication safety should be a standing item in the regular patient safety staff meetings and be a key part of your practice's patient safety plan. Most importantly, these various parties have to understand their respective role in ensuring the safety of medication beyond hospital settings.

Chapter Eleven: Biosimilars, Pharmacovigilance, and Challenges in Yemen

11.1. Introduction:

A biosimilar is a biological product similar to a biological agent already approved by the FDA, the so-called reference product. It may be tempting to think of a biosimilar as a "generic" version of the reference product. However, there are many significant differences between biosimilars and generic versions of traditional (generic) drugs. A generic is chemically identical to its brand: an exact copy. The generic and brand-name drug has the same active ingredient, dosage form, safety profile, dosage, route of administration, performance characteristics, and intended use. Consequently, the brand name drug and the generic drug are considered bioequivalent.

A biosimilar is not an exact duplicate of another biological. All organic products have some natural variability. It is not possible to make an exact copy of a living cell product. All organic products, including reference products, have some variations from lot to lot. A biosimilar may have a different structure than the reference product, but the active ingredients are essentially the same in molecular and biological terms. This means that there are no clinically significant differences between biosimilar medicine and the reference product in terms of safety or efficacy. Only small differences in the clinically inactive components are allowed.

The first biosimilar product in the United States, Zarxio, was approved in March 2015 and launched in September 2015. Zarxio (filgrastim-sndz) is a biosimilar of Neupogen (filgrastim), a drug that

reduces the risk of infections in patients with certain types of cancer undergoing chemotherapy which reduces the number of white blood cells. More than 50 biosimilar products are currently under development. Some experts pointed their discussion on the following points:

- **Estimation of Efficacy and Safety of Drugs from Structure**

The experts were aware of structural differences between the original and the biosimilar may have an undesirable effect on the effectiveness and safety of the biosimilar. The experts also stressed the discovery of all manufacturing steps for the biologicals because they concern the quality of the biosimilar product. The compounds' biophysical properties could not reflect clinical efficacy and patient safety. So, giving that the structure of particular molecules is not identical, there must be proper clinical studies with overall efficacy and safety approval for biosimilars to pass the regulatory barriers, particularly in treatments with remedial purpose where the effect of the drug cannot be measured in an individual patient.

- **Justification and Extent of Extrapolations**

Commonly, the development programs of biosimilars are not directed through all the indications for which the authentic biological was accepted. Consequently, dose it is safe to extrapolate the existing clinical efficacy and safety data for the biosimilar products through identical indications as to the original ones. For monoclonal antibodies, the EMA guidelines declared that extrapolation of clinical efficacy and safety data to other indications of the reference monoclonal antibody, although not exactly studied throughout the clinical development of the biosimilar monoclonal antibody, is probably built on the complete indication of comparability based on the comparability exercise and with satisfactory explanation [146]. The experts documented the difficulties related to the extrapolation of data to clinical situations not

considered. Attention is necessary regarding evaluating the efficacy and safety of a biosimilar to a different degree:

- Low problems may be occurred due to some extrapolations: e.g. epoetins, because for these compounds, the elevation in hemoglobin after administration is a PD marker, following the EMA guideline [146].
- Other problems were encountered e.g. the use of G-CSF in bone marrow transplantation, stating to the World Marrow Donor Association position paper which warned about the extrapolation of efficacy data from the autologous transplant setting to that of allogeneic transplantation [147].
- The following areas may not be acceptable to clinicians:

– Extrapolation across disease entities: e.g. extrapolating data from rheumatoid arthritis to Crohn's disease (although both are inflammatory diseases).

– Extrapolation across different phases of the same disease (from palliative to curative). Can, i.e. the efficacy of biosimilar trastuzumab in metastatic disease be extrapolated to its use in early breast cancer?

11.2. Pharmacovigilance of Biosimilars

Biosimilars as defined by the FDA: "A biosimilar is a highly productive biological product despite an organic reference product approved in the USA small differences in clinically inactive components and for which there are no clinically significant differences between the biological one's reference product and product in terms of safety, purity and product efficacy "[148].

So these biosimilar products are affordable alternatives to several biotech products that are loss of patent. Along with the advantage of inexpensive therapy and the extension of further research leading to the possibility of organic supervisors. Biosimilars have created an entirely new branch of the biotechnology Industry. However, there are various other

concerns that these justify biosimilars need to be closely monitored. The European Medicines Agency (EMEA) has published a guideline

Special emphasis should be placed on pharmacovigilance, taking into account the limited number of patients studied during the registration process of biosimilars. Companies introducing biosimilars should therefore set up a risk-management/pharmacovigilance plan. The objective can be achieved through collaboration with patient registries that have been established in several countries. The risk-minimization activities for the biosimilar should be comparable to those of the reference medicinal product.

Aspects which should be covered in the risk-management/pharmacovigilance plan include:

- Safety assessments, including rare and serious adverse events, are described and predicted, based on the pharmacology and experience with the original.
- The plan should ensure that any novel safety signals are captured.
- Accurate assessment of immunogenicity data: since immunogenic reactions may arise only in a small number of patients, clinical data monitoring systems must be put in place.
- Clear traceability and identification of the drug (original or biosimilar) associated with an adverse event.

"Similar Biological Medicines" in October 2005 and ever since 14 biosimilar products have been approved by the EMA for Europe Market. This includes the biologics of three main classes: human growth hormone, granulocyte colony-stimulating factor, and erythropoietin [149]. Considering the need for biosimilars for the USA's current market, the FDA recently released a draft guideline in 2010 to try to do this provide a licensing path for biosimilars. The guide is intended to ensure the safety, purity, and efficacy of these biosimilars before approval. Unlike generics for small molecules, biosimilars

are is subject to rigorous regulatory process Several negative effects can be produced during the synthesis of these biosimilar products. So in contrast to small-molecule generics, approval of biosimilars requires clinical trials_to ensure that small changes in the production of_therapeutic efficacy of the biological drug. Also, pharmacovigilance

allows the monitoring of side effects associated with a particular one marketed biosimilar [147].

The World Health Organization (WHO) defines pharmacovigilance such as "science and activities related to the detection, evaluation, Understanding and preventing side effects or other drug-related side effects problem. "[150]

As soon as a drug is approved by the FDA, the drug is said to generate post-market surveillance data. Post-marketing pharmacovigilance is becoming an even more important case of biosimilars as limited information is available. Furthermore, the effect of these biosimilars on different patient populations concerning dosage and duration of therapy must be carefully monitored. For

these reasons, biosimilars are needed to subject to the same pharmacovigilance regulations as the reference product. Therefore, EMEA approved biosimilars must present a Risk Management Plan (RMP) together with a marketing application regular security update reports should be sent after the product has been released to the market. The RMP contains and suggests the safety profile of the drug prospective pharmacovigilance studies [151].

Biosimilars are currently approved for the European market under strict pharmacovigilance to ensure patient safety. Ebbers et al. [152] report on several pharmacovigilance activities carried out to monitor the safety of such approved biosimilars. These efforts include cohort studies and side effect monitoring surveys effects of erythropoietin biosimilars, pharmacovigilance programs safety follow-up for long-term data on the use of granulocytes

colony-stimulating factor, and a review of immunogenicity data for human growth hormone administered to the younger population [151].

Along with these studies, the spontaneous monitoring of adverse events effects is meant to be useful. Spontaneous reports since Healthcare professionals help identify the responsible biological agent it, target patient population, the severity of the side effect needs for intervention. Overall, these surveillance studies are capable to generate information that is not only useful for the patient

The population in Europe, however, also supports the data in this regard with scientists in other countries such as the USA, where several biotechs/pharmaceutical companies plan to be involved in the biosimilar field. In summary, pharmacovigilance is an essential part of biosimilars approval because these biologics are not small molecular generics. Pharmacovigilance studies will continue to be valuable for the biotech industries to provide safe and effective organic products to the market as a data pool is growing in terms of its safety profile of some of the approved biologics.

11.3 Drug regulation in Yemen:

In general medicine regulations and legislations aims to ensure the quality, safety, efficacy of medicines, and accuracy of medical information. It is developed, implemented, monitored, and re-enforced by Medicine Regulatory Authority (MRA). The government of Yemen granted the power of responsibility to the MRA. MRA is responsible for the registration of medicines; importation, distribution, and sales of medicines; medicine promotion; licensing of pharmaceutical establishments, their staff, and performance; pharmaceutical quality assurance; commitment to Good Manufacturing Practice (GMP) and regulation enforcement. The SBDMA is the main MRA in the country. It is a semi-autonomous agency concerned mainly with authorizing marketing, importing, and manufacturing control; providing licenses for medicines, medicine producers, and wholesalers; controlling the medicine market, and controlling the quality and pharmacovigilance of the imported medicines and medical appliances[54]

In the last five years, the medicines regulatory system has been placed under proper assessment. The SBDMA receives funding from the government budget and retains its revenues from regulatory activities as well. However, the apparent limitation of MRA was its inability to distribute a list of the registered products, updating the names of the products regularly to provide a reliable source about the authorized products which are officially available in the country. The Profile further revealed that there was a guide being published for the registered pharmaceuticals. Unfortunately, this guide had not been updated for more than a decade. Registration and authorization are paramount for the public to feel ‘safe’ about using the medicines that are suitable to their health and needs, but the seemingly lackadaisical attitude of the authority regarding marketed medicines and pharmaceuticals updates have created loopholes in the

11.4. Current pharmacovigilance program in Yemen

At present, the monitoring of adverse drug reactions was launched in Yemen by establishing a pharmacovigilance center in 2011. Currently, there is few published information about its activities, number of reports, and how they process reported documents. The country and public are encountered with many safety problems related to drug smuggling, counterfeit drugs, improper and irrational use of drugs, importation of unnecessary drugs, and medical errors. Therefore, it is necessary to take serious steps and clear regulations in Yemen to ensure patients and public safety concerning medicines use.

Academics from the Faculty of Pharmacy at Aden University accompanied with appointed representatives of SBDMA in Aden recently decided to initiate a pharmacovigilance program in Yemen, to activate the pharmacovigilance center of SBDMA to cover the whole country and to establish a plan to implement the basic steps for the establishing pharmacovigilance program according to Uppsala Monitoring Centre (UMC) Guidelines.

Activities began towards the end of 2014 by reviving of the center, designing a website and reporting forms for HCP and consumer .to raise the awareness among HCP and consumers. many articles in Yemeni journals were published as well as many posters were distributed in hospitals to achieve the desired objective. Several educational interventions were conducted among HCP in hospitals and teaching pharmacovigilance for pharmacy students at Aden University and conducting research activities in pharmacovigilance. Dr. Alshakka has studied the current practices of pharmacovigilance when he conducted study for CPDs in Aden [162]. He concluded that they have poor KAP towards ADR reporting and pharmacovigilance. Participants have

insufficient knowledge about pharmacovigilance practices, operation, purpose, and usefulness. The results emphasized the importance of continuing efforts to promote the ADR program to ensure patient and public safety concerning medicine use. Education and training of health professionals and the public will be important in increasing and maintaining ADR reporting. In another paper, Alshakka et al found that a relatively good level of pharmacovigilance knowledge has been encountered among physicians and nurses [54].

The National Center follow up drugs after marketing, assess the quality of pharmaceuticals, disclosure of side effects, and evaluate and develop solutions leading to prevent these incidents, and receive communications on this matter, as well as the follow-up news from international bodies and organizations to make appropriate decisions about the safety of pharmaceuticals traded.

Taking in account, the fact that the public is not fully aware of the risks of medicines and the possibility of their misuse and abuse, the government of Yemen has decided to dispense drugs only by prescriptions except some medicines which can be dispensed without prescriptions namely over-the-counter (OTC) medicines. However, The MOPHP and the Supreme Board of Drugs and Medical Appliances (SPDMA) showed incompetence to regulate, control, and monitor the prescriptions. Generally, people in Yemen may not have been very well informed about the potential effects of drugs, and dispensing medication without a valid prescription is common practice in this country. All medicines including prescribing-only medicines (POM) such as antibiotics, antipsychotics, cardiovascular drugs could be obtained without a prescription from pharmacies. Pharmacies are mostly run by pharmacy technicians and untrained dispensers, probably due to few qualified pharmacists. Thus we cannot expect that the

pharmacy staff would comprehend the detailed impact of a drug they are selling to customers. The tragic situation when those dispensers are misinterpreted as 'physicians' for the customers, as they involved many times in diagnosis, prescribing, and dispensing medicines for various health complications and diseases, despite their ill knowledge and against authority rules. This repeated professional misconduct must be rectified. Rational use of medicines aims to improve the use of medicines by health providers, individuals, and communities through rational prescribing, dispensing, and appropriate use of individuals and the community.

Therefore, it is necessary to implement strategies to ensure patients and public safety concerning medicines use. In developing countries generally, there is limited coverage and under-reporting of ADRs.

The effectiveness of pharmacovigilance activities in a country is directly dependent on the active participation of health professionals, patients, and consumers. The more information about ADRs is collected the better it will definitely lead to more useful outcomes as a national database. Therefore, all should be briefed regarding the ADRs reporting system and encouraged to report ADRs even suspected ones.

11.5. Important of Pharmacovigilance of Biosimilars in Yemen

Improving the pharmacovigilance for biosimilars should be aware by the Physicians and researchers. A report by researchers in India highlighted the complexity and temperature sensitivity of biosimilars. Biosimilars have a large multipart structure, several industrial processes, and are made in a living organism, which means that they necessitate distinct delivery devices and limited temperature controls to avoid degradation. Biosimilars require more extensive pharmacovigilance measures than generics and at least the same level of pharmacovigilance

as their reference products. The researchers also, recommend the continuation of the studies and pharmacovigilance reporting while a biosimilar is on the market, as the composition of patient populations can change and drug reliability can differ over time. Appropriate monitoring and risk management are essential for good pharmacovigilance practice which requires reporting all types of suspected reactions, proposed drug-drug interactions or drug-food interactions, adverse drug reactions [ADR] related to drug discontinuation, medication errors, or overdosing to regulatory authorities' ineffectiveness.

A comprehensive pharmacovigilance program should include regular safety update reports and risk management plans. Many variables can affect the quality of the active ingredient of biosimilars while the transition from plant to clinic to the patient even if their manufacturing processes are safe and efficient. Patent problems can also influence the kinds of dispensing devices that can be used. Also, the volume and quality of the drug delivered can be affected by the delivery device due to close contact between the active ingredients and the delivery device. Therefore, the safety of the device delivery system for biosimilars is of dominant importance.

The temperature is among the most important environmental parameter. Pharmacovigilance should take consideration of this point, which is commonly ignored until a problem like lack of efficacy or immunogenicity is recognized. Many authors recommend that pharmacovigilance concerning temperature should extend to transport and storage conditions. Yemen has some active substance for biosimilars registered by SBDMA as listed in Tabel 1. Here the first biosimilar was marketed for Erythrobiotin, The several-step manufacturing procedure for

biosimilars is liable to variations that will affect the final drug, including immunogenicity, an important safety risk associated with biosimilars. The manufacturing process for biosimilars is recognized to affect the level of process-induced contamination and post-translational modifications of the product.

Biosimilars, like generics, are given by injection rather than orally, increasing safety and liability concerns about the delivery device. Some authors recommend monitoring manufacturing devices and assessing factors such as ease of use that could affect patient compliance. The researchers notice that rare adverse reactions frequently occur when large numbers of patients use a biosimilar. Consequently, biosimilars need post-market observation and possibly post-authorization studies to assess identifying formerly unidentified adverse drug reactions and to better evaluate the risks and benefits of a drug. Suitable pharmacovigilance requires expert and qualified personnel (as with original biological products) due to the complexity of safety data and the difficulty of detecting adverse reactions.

11.6.Conclusions

the availability of biosimilars as lower-cost biologics must wisely consider issues of safety, efficacy, and traceability. Strict pharmacovigilance procedures are needed to evaluate the potential differences in safety indications between biosimilars and their reference products and recognize the adverse drug reactions with biologics and biosimilar products. Pharmacovigilance of biologics should contain procedures that are straightforwardly used by prescribing practitioners to guarantee that data are reliable and new safety signals are appropriately reported and allocated to the precise and accurate product

11.7. Recommendations

Some recommendations should be followed by the interested parties to enhance approval and safe use of biosimilars:

1. Evaluation and analysis of the biosimilars by the regulatory authorities should be improved. Staff should have suitable skills and expertise, also knowledge sharing between the health authorities is a must.
2. Working groups should be established in different parts of Yemen under the supervision of the Minister of Public Health and Population to share their regulatory experience and plans related to biosimilars.
3. Each governorate in Yemen should establish its working group, including experts with interest in biosimilars, to support regulatory authorities in their efforts to introduce biosimilars into their particular governorates.
4. The pharmacovigilance efforts should be encouraged by training health staff and increasing awareness about reporting the adverse effects of drugs including the biosimilars and analyzing the related data.
5. Products that were accepted as 'intended copy' biological drugs should be assessed according to regulations specific to biosimilars. It should not be supposed that a previously accepted biopharmaceutical is definitely a biosimilar, irrespective of existing clinical experience. Reconsideration is important and the pharmaceutical company should carry the required studies on time.

Tabie 1. List of Active Substance for Biosimilars in Yemen

NO	Generic name	Product	Dosage form	Agent	
1	Human albumin	ZENALB (TM)	Oral solution	AL-SALAMAH MEDICAL & TRADING CO. LTD	BIO PRODUCT LABORATORY (BPL) [UNITED KINGDOM]
2		ALBAPURE	Vial	ETHMAR TRADING LTD	CROMA PHARMA GMBH AUST(MA)P.F(RAFAA) [AUSTRIA]
3		HUMAN ALBUMIN	Iv injection	AL-MADINA MEDICAL CORPRATION	FARMACUBA [CUBA]
4		ALBUTEIN	Iv injection	ASHARQ TRADE & AGENCIES & OIL FIELDS SUP	GRIFOLS [UNITED STATES OF AMERICA]
5		HUMAN ALBUMIN	Iv Injection	BILQUIS DRUGS STORES	HUMAN BIOPLAZMA MANUFACT.&TRADING LTD . [HUNGARY]
6		UMAN	Vial	NASHWAN PHARMA CO LTD	KEDRION S.P.A [ITALY]
7		YDR ALBUM	Iv injection	AL-NAHDI .MEDICALS CO	L.F.B. [FRANCE]
8		HUMAN ALBUMIN	Iv Injection	AL-FATH TRADING CO. .Ltd	OCTAPHARMA [AUSTRIA]
9		PLASBUMIN-20	Iv Injection	SALLAM-PHARM TRADING	TALECRIS BIOTHERAPEUTICS [UNITED STATES OF AMERICA]

10	Human albumin	HUMAN ALBUMIN	Iv Injection	ARRA'AFAH CORPORATION FOR DRUGS	BAXTER AG VIENNA AUSTRIA(RAFFAA) [AUSTRIA]
11		BUMINTE	Iv Injection	ARRA'AFAH CORPORATION FOR DRUGS	BAXTER HEALTHCARE CORPORATION USA [UNITED STATES OF AMERICA]
1	Anti-tetanus injection	TETANUS TOXOID	Ampoule	SISCO FOR MEDICINE&MEDICAL SUPP.CO.Ltd	SERUM INSTITUTE [INDIA]
2		TETANUS ONTI TOXIN	Vial	NAGIB A	VINS BIOPRODUCTS LIMITED [INDIA]
1	ERYTHROPOIETIN injection	EPOFORM	Vial	AL-MEITEMI CORPORATION FOR DRUGS	EIPICO [EGYPT]
2		EPOTIN	Vial	ARD AL-GANNATEIN COMPANY	JULPHAR [UNITED ARAB EMIRATES]
3		EPOETINE	Vial	AL-HARETH CORP. FOR DRUGS & MEDICINES	SEDICO [EGYPT]
1	Essential amino acid injection	ANOSOl	Iv Injection	AL-MEITEMI CORPORATION FOR DRUGS	SHIN POONG PHARMACEUTICAL CO. LTD [REPUBLIC OF KOREA]
2					
3		HIKMEN	Iv injection	ABDUL HAFEED THABET SAIF HOUSES	BORYUNG PHARMA [REPUBLIC OF KOREA]
4		LEVOTASOL			
5		MARINASOL	Iv injection	AL-MEITEMI CORPORATION FOR DRUGS	CHONG KUN DANG PHARMA [REPUBLIC OF KOREA]
6		RUCHIASOL			
7		CELEMIN 10 .PLUS	Iv Injection	ALABED MEDICAL SUPPLIES CO.LTD	CLARIS LIFESCIENCES [INDIA]
8		CELEMIN 5-S			
9		NEPHRISOL	Iv injection	CRESCENT CANDLE FOR TRADING	DAIHAN PHARMA.CO.,LTD. [REPUBLIC OF KOREA]
10		SAERONAMIN			

11	Essential amino acid injection	AMINOLEBAN	Iv injection	AL-FATH TRADING CO. .Ltd	OTSUKA (EGY) [EGYPT]
12		PAN-AMIN G			
13		PAN-AMIN SG			
1	Heparin injection	HEPARIN SODIUM	Iv Injection	MOHAMMED MAHDI AL-.SHAER CORP	PANPHARMA [FRANCE]
2		HEPARIN-Na	Vial	ARRA'AFAH CORPORATION FOR DRUGS	SANDOZ GMBH [AUSTRIA]
3		HEPARIN-Ca	Ampoule		
4		HEPARIN	Vial	AL-MEITEMI CORPORATION FOR DRUGS	SHIN POONG PHARMACEUTICAL CO. LTD [REPUBLIC OF KOREA]
5					
6		RINHEPA	Vial	BAUAM BROTHERS .TRADING EST	United biotech(P) [INDIA]
7					
8		UNIPARIN-Ca	Vial	HILAL PHARMACY	WOCKHARD(MANUFCT. CP PHARMACEUTICAL UK) [UNITED KINGDOM]
9		UNIPARIN-Na			
10		HIKMA-HEPARIN	Vial	ARD AL-GANNATEIN COMPANY	AL-HIKMA [JORDAN]
11					
12					
13		HEPARODIC	Ampoule	MAGNICO FOR TRADING & .AGENCIES	CASPIAN TAMIN [ISLAMIC REPUBLIC OF IRAN]
14		ARAPIN	Vial	ALABED MEDICAL SUPPLIES CO.LTD	CLARIS LIFESCIENCES [INDIA]

15	Heparin injection	HEPARIN	Vial	SISCO FOR MEDICINE&MEDICAL .SUPP.CO.Ltd	GLAND PHARMA [INDIA]
16		VAXCEL HEPARINE	Vial	DADIAH GENERAL TRADING	KOTRA PHARMA(M)SDN.BHD [MALAYSIA]
17		HEPARIN Na	Vial	ASHARQ TRADE & AGENCIES & OIL FIELDS SUP	LEO DENMARK [DENMARK]
18		HEPARIN-LEO			
1	Serum & vaccine	DIPHTHERIA TET. VAC. ADU	Ampoule	SISCO FOR MEDICINE&MEDICAL SUPP.CO.Ltd	SERUM INSTITUTE [INDIA]
2		DIPHTHERIA TET. VAC. PED			
3		DIPHTHERIA TETANUS PERTUS			
4		MEASLES, MUMPS & RUBELLA			
5		MEASLES VACCINE, LIVE			
6		POLYVALINT ANTI-SNAKE VEN			
7		RABIVAX			
8		RUBELLA VACCINE			
9		SCORPION VENOM ANTISERUM	Vial	NAGIB A	VINS BIOPRODUCTS LIMITED [INDIA]
10		SNAKE VENOM ANTISERUM			
11		VINRAB			
12					
13		SNAKE VENOM .ANTISERUM	Vial	ALFA PHARMA. COR	BHARAT SERUM&VACCINES Ltd [INDIA]

1	Immunoglobulin Human	OCTAGAM	Iv Injection	AL-FATH TRADING CO. Ltd	OCTAPHARMA [AUSTRIA]
2		EQUIRAB			
3		RHOCLONE FREEZE DRIED	Iv Injection	ALFA PHARMA. COR	BHARAT SERUM&VACCINES Ltd [INDIA]
1	Insulin	INSUGEN - 30/70(biphasic)	Vial	AL-KHALIL FOR DRUG	BIOCON LIMITED [INDIA]
		INSUGEN-N ISOPHAN			
2		INSUGEN-R SOLUBLE			
3		JUSLINE	Vial	ARD AL-GANNATEIN COMPANY	JULPHAR [UNITED ARAB EMIRATES]
4		JUSLINE N			
5		JUSLINE R			
6		ACTRAPID HM	Vial	ARRA'AFAH CORPORATION FOR DRUGS	NOVO NORDISK [DENMARK]
7		ACTRAPID NOVOLET			
8		INSULATARD HM			
9		INSULATARD NOVOLET			
10		MIXTARD			
11		MIXTARD 30 HM			

12	Insulin	APIDRA SOLOSTAR	Ampoule	NATCOPHARMA	SANOFI AVENTIS GERMANY(NATCO) [GERMANY]
13		LANTUS	Vial		
14		INSULIN H BIO NPH	Vial	AL-HARETH CORP. FOR DRUGS & MEDICINES	SANOFI AVENTIS GERMANY(NATCO) [GERMANY]
15		INSULIN H MIX			
16		INSULIN H BIO R			
17		INSULET NPH	Vial	BAWAM FOR MEDICINES	SOTHEMA [MOROCCO] VACSERA [EGYPT]
18		INSULET RAPID			
19		HUMAN .INSULIN MIX	Vial	AL-FATH TRADING CO. Ltd BAWAM FOR MEDICINES	VACSERA [EGYPT]
20		HUMAN INSULIN R			
21		HUMAN INSULIN N			

Chapter Twelve - Resources for Pharmacovigilance Literature

Books

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Journals

1. BMJ (British Medical Journal).
2. The New England Journal of Medicine.
3. The Lancet.
4. JAMA (Journal of the American Medical Association).
5. Drug Safety.
6. Pharmacoepidemiology and Drug Safety.
7. The International Journal of Risk & Safety in Medicine.
8. Reactions Weekly.
9. Prescrire.
10. Drug Information Journal.
11. ADR Newsletters from National Centres.
12. Pharmacoepidemiology& Drug Safety.

WHO-UMC publications

1. Safer Medicines, Safer Use of Medicines, Safer Patients (leaflet).
2. Aide Memoire - For a National Strategy for Safe Drugs and Their Appropriate Use.
3. WHO Policy Perspectives on Medicines no. 9 - PV: Ensuring the Safe Use of Medicines.
4. Viewpoint (part 1).
5. Viewpoint (part 2).
6. The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products.
7. Safety Monitoring - Guidelines for Setting Up and Running a Pharmacovigilance Centre.
8. Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions.
9. Being a Member of the WHO Programme.
10. Uppsala Reports (Newsletter).
11. Vigiflow - when time is crucial (leaflet).
12. VigiSearch/VigiMine (leaflet).
13. CemFlow (leaflet).
14. SIGNAL.
15. WHO Pharmaceuticals Newsletter.
16. WHO Drug Information.

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25. Accepted Scientific Names of Therapeutic Plants and their Synonyms.
26. Herbal ATC Guide.
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