



**HAL**  
open science

# Analysis of the medicines panorama in Pakistan: The case of antimicrobials: market offer width and consumption

Farrukh Javaid Malik

► **To cite this version:**

Farrukh Javaid Malik. Analysis of the medicines panorama in Pakistan: The case of antimicrobials: market offer width and consumption. Human health and pathology. Université de Bordeaux, 2019. English. NNT: 2019BORD0266 . tel-02887504

**HAL Id: tel-02887504**

**<https://theses.hal.science/tel-02887504>**

Submitted on 2 Jul 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**ANALYSIS OF THE  
MEDICINES PANORAMA IN  
PAKISTAN**



**THE CASE OF ANTIMICROBIALS:  
MARKET OFFER  
WIDTH AND CONSUMPTION**

Farrukh Javaid Malik

THESIS PRESENTED TO OBTAIN THE GRADE OF

**DOCTOR OF THE UNIVERSITY OF BORDEAUX**  
**Doctoral School, SP2: Society, Politic, Public Health**  
**Specialization Pharmacoepidemiology and Pharmacovigilance**

By Farrukh Javaid Malik

**“Analysis of the medicines panorama in Pakistan –  
The case of antimicrobials: market offer width and consumption.”**

Under the direction of  
Prof. Dr. Albert FIGUERAS

Defense Date: 28<sup>th</sup> November 2019

**Members of Jury**

M. Francesco SALVO, Maître de conférences des universités – praticien hospitalier, Université de Bordeaux	President
M. Albert FIGUERAS, Professeur des universités – praticien hospitalier, Université Autonome de Barcelone	Director
Mme Antonia AGUSTI, Professeure, Vall d'Hebron University Hospital	Referee
Mme Montserrat BOSCH, Praticienne hospitalière, Vall d'Hebron University Hospital	Referee

## **Abstract**

A country's medicines market is an indicator of its healthcare system, the epidemiological profile, and the prevalent practices therein. It is not only the first logical step to study the characteristics of medicines authorized for marketing, but also a requisite to set up a pharmacovigilance system, thus promoting rational drug utilization.

The three medicines market studies presented in the present document were conducted in Pakistan with the aim of describing the characteristics of the pharmaceutical products available in the country as well as their consumption at a national level, with a special focus on antimicrobials.

The most important cause of antimicrobial resistance is the inappropriate consumption of antimicrobials. The results of the researches conducted in Pakistan showed some market deficiencies which could be addressed as part of the national antimicrobial stewardship programmes.

## Résumé

Le marché du médicament d'un pays est un indicateur de son système de santé, de son profil épidémiologique et des pratiques [de prescription] qui y règnent. Il ne s'agit pas seulement de la première étape logique pour étudier les caractéristiques des médicaments autorisés à la commercialisation, mais aussi d'une condition préalable pour la mise en place d'un système de pharmacovigilance qui favorise une utilisation rationnelle des médicaments.

Les trois études de marché sur les médicaments présentées dans le présent document ont été réalisées au Pakistan avec l'objectif de décrire les caractéristiques des produits pharmaceutiques disponibles dans le pays ainsi que leur consommation au niveau national, en mettant un accent particulier sur les antimicrobiens.

La principale cause de résistance aux antimicrobiens est leur consommation inappropriée. Les résultats des recherches menées au Pakistan ont révélé certaines lacunes dans le marché qui pourraient être comblées dans le cadre des programmes nationaux de gestion des antimicrobiens.

## Acknowledgements

First and foremost, I begin in the name of **ALLAH** the most merciful the beneficial, who granted me the primary inspiration and motivation all along to complete this manuscript and the preliminary research. There were invaluable contributions by many people, & I sincerely “thank” them all as it is difficult to express my gratitude in a few lines.

I am incredibly grateful to my parents, Mr. Muhammad SHAFI (Late) & Mrs. Khizrat BIBI, for all their sacrifices to raise me with an opportunity to get the best possible training & education. They encouraged, supported, and motivated me to progress all along, especially during my father’s brave 4.5-year fight with cancer, they both kept me going & didn’t let me give up. For all the reason together, this was only possible because of their prayers, and my father’s wish to finish this before he left us in 2018. I miss you & wish you were here with us to the completion of this work.

I especially want to thank my supervisor, Prof. Albert FIGUERAS, for generously guiding all aspects of this manuscript, for continuously encouraging me and pushing me to complete my thesis. The empathetic support you gave me through the difficult times with my father’s illness to my thesis completion is incredibly invaluable. I thank Eu2P and the University of Bordeaux for the opportunity to study the subject I have been so passionate about and especially in the context of Pakistan.

To my ever-supportive partner, my wife Hirah MALIK, without you, this was never possible. Your continuous invaluable inputs despite this not being your main subject and the unwavering encouragement has immensely contributed to complete this work. I am grateful that I have you all this time. I thank you for your undying, love, and support and for believing in me that I can finish my manuscript on-time. I thank my sons Zayyan MALIK & Issa MALIK for all the joy, hope, and laughter you bring to my life.

My beloved sisters Farah MALIK and Fiza MALK, even if you both were not physically with me, but I know from my heart, you were with me in spirit. Thank you for all the support, love, and prayers. I love you both and the little Zariya and Zaviyar.

I am thankful to friends, including Dr. Junaid Bhatti, Mr. Ayyaz Kiani, Mr. Muzammil Malik, Mr. Abdul Samad, Dr. Tayyaba Khan, Dr. Hafiz Alam Sher, Dr. Asma Amjad, & Dr. Imane Khireddine for all their insights, suggestions, comments and discussions to improve this work. I thank you for entertaining even my trivial questions, and for bearing with all my queries.

I am grateful to Mr. Haroon Qassim, Mr. Jamshed Ahmed, Dr. Zakiuddin Ahmed, Dr. Abdul Malik, Dr. Abid Jamal, for believing and encouraging me in many ways to keep going and finishing this project. Special thanks to PharmEvo Pvt. Ltd and IQVIA for the sales data. I thank OTWO for their design work.

Lastly, special appreciation & acknowledgment for Mr. Naveed Bhatti & Mr. Waseem Bhatti, who lent their unconditional support at all times. I truly value your contributions & have the deepest gratitude, bless you, brothers, and my little niece Amna and nephew Abdullah.



## Declaration of Good Academic Conduct

"I Farrukh J. Malik hereby certify that this dissertation, which is 24823 words in length, has been written by me, that it is a record of work carried out by me, and that it has not been submitted in any previous application for a higher degree. All sentences or passages quoted in this dissertation from other people's work (with or without trivial changes) have been placed within quotation marks, and specifically acknowledged by reference to the author, work, and page. I understand that plagiarism, the unacknowledged use of such passages will be considered grounds for failure in this dissertation and in the degree programme as a whole.

I also affirm that, with the exception of the specific acknowledgments, the following dissertation is entirely my own work."



.....  
Farrukh J. Malik  
Date: 16 October 2019



# Table of Contents

Abstract	iii
Résumé	iv
Acknowledgements	v
Declaration of Good Academic Conduct	vii
Table of Contents	viii
Table of Figures	xi
Table of Tables	xi
List of Abbreviations	xii
Definitions of Key Concepts	xiv
Chapter 1 : Introduction	1
1.1 Different medicines markets	4
1.2 Harmonised Regulatory Actions	6
1.3 Globalization	7
1.4 Added Value of Medicines	8
1.5 Prescription & Dispensing	9
1.6 Rationalizing antibiotic usage through protocols based on standard Guidelines	11
1.7 Use of Medicines	11
1.7.1 Irrational Use	12
1.8 Cleaning the Medicines Market	14
1.9 Fixed Dose Combinations	14
1.10 Summary	16
1.11 Objectives of the study	17
1.12 References	20
Chapter 2 : Methodology	26
2.1 Drug Utilization Studies	27
2.2 Type of Drug Utilization Studies	27
2.3 Drug Utilization Data:	28
2.4 Classification of Medicines:	29
2.5 Units of Measurement:	30
2.6 IQVIA	30
2.7 Study 1: Antimicrobials in Pakistan	31
2.8 Study 2: Cephalosporins & Fluoroquinolones Consumption	32
2.9 Study 3: Fixed dose Combinations in Pakistan	32
2.10 References	35

Chapter 3 : Analysis of the Antimicrobial Market in Pakistan: Is It Really Necessary Such a Vast Offering of “Watch” Antimicrobials?	38
3.1 Abstract	39
3.2 Introduction	40
3.3 Materials and Methods	42
3.4 Results	43
3.5 Discussion	46
3.6 Conclusion	48
3.7 References	50
Chapter 4 : Continuous rise in cephalosporin and fluoroquinolone consumption in Pakistan: a 5 year analysis (2014 – 18)	53
4.1 Abstract	54
4.2 Introduction	55
4.3 Methods	56
4.4 Results	57
4.4.1 Cephalosporin consumption	57
4.4.2 Fluoroquinolone consumption	60
4.5 Discussion	60
4.6 Conclusion	62
4.7 References	63
Chapter 5 : Analyses of the registered fixed-dose combinations in Pakistan: a first step to improve the rational use of medicines	65
5.1 Abstract	66
5.2 Introduction	67
5.3 Methods	68
5.3.1 Consumption data source	68
5.3.2 Analysis of fixed-dose combinations	69
5.4 Results	72
5.4.1 Consumption of FDCs in Pakistan	75
5.5 Discussion	76
5.5.1 A Rising Trend of Fixed Dose Combination Prescribing Pattern	80
5.6 Conclusion	81
5.7 References	83
Chapter 6 : Discussion	86
6.1 Putting the results into context	88
6.1.1 Pharmaceutical Industry in Pakistan	88
6.1.2 The paradox of a big market width and shortage of medicines	89
6.2 Adopting drug utilization studies methodology in Pakistan	89
6.3 Available medicines as a first step to rationalize the consumption of medicines	90
6.4 From the volume-based market to value-based market	91

6.5	Limitations of Using Sales Data for Analysis	92
6.6	Recommendations to Counter Irrational Drug Prescription Patterns	94
6.6.1	Short Term Targeted Approach	94
6.6.2	Long Term System-Based Approach	95
6.6.3	Regional Recommendations with other countries	97
6.7	References	98
Chapter 7 : Conclusions		99
Too much & too little about medicines in Pakistan		101

## Table of Figures

Figure 1: Tiers of the pharmaceutical supply chain in Pakistan and key stakeholders.	5
Figure 2: Possible implications of the irrational use of medicines.	13
Figure 3: Classification of Cephalosporins and Fluoroquinolones under ATC.	29
Figure 4: Figure Explaining the Methodology of the Conducted Studies.	34
Figure 5: Distribution of the number of brands of all Antimicrobials for systemic use present in the country according to the ATC classification, according to the WHO AWaRe classification.	44
Figure 6 : Five year DID sales trend for 'Access', 'Watch', & 'Reserve' Cephalosporins in Pakistan.	58
Figure 7 : Flowchart explaining the research approach.	71

## Table of Tables

Table 1: Top 20 antimicrobials not considered in the WHO-EML but available in the Pakistan market according to the number of brands and presentations per active ingredient and classified according to the WHO <i>AWaRe</i> categories. ....	45
Table 2 : Evolution of the sales of Cephalosporins and Fluoroquinolones in Pakistan expressed in defined daily doses/1,000 inhabitants/day (DID) during the study period.....	59
Table 3 : Distribution of approved fixed dose combinations according to their ATC classification....	74
Table 4: Highest Selling Unjustified Fixed-Dose Combination in Pakistan's Medicine Market.....	79

## List of Abbreviations

ADR	Adverse Drug Reactions
AM	Antimicrobials
AMR	Antimicrobial Resistance
ATC	Anatomic therapeutic chemical classification
CMA	Conditional marketing authorisation
CME	Continued Medical Education
CIMS	Current index of medical specialties
CTD	Common technical document
CVD	Cardiovascular disease
DDD	Defined daily dose
DID	Defined daily dose for 1000 people/day
DRA	Drug Regulatory Authority
DRAP	Drug Regulatory Authority of Pakistan
EBM	Evidence based medicine
EMA	European Medicines Agency
FDA	Food and Drug Authority
HER	Electronic Health Records
FDC	Fixed-Dose Combination
ICESC	International Covenant on Economics Social & Cultural Rights
INN	International Non-proprietary Names

LMIC	Low and middle-income countries
NDMA	N-nitrosodimethylamine
PASS	Post-authorisation safety studies
PE	Pharmacoepidemiology
PEML	National Essential Medicines List of Pakistan
PKPI	Pakistan Pharmaceutical Index
PMDA	Pharmaceutical and medical devices agency
PV	Pharmacovigilance
RWE	Real world evidence
WEML	World Health Organization's Essential Medicines List
WHO	World Health Organization
WHO-UMC	Uppsala Monitoring Centre

## Definitions of Key Concepts

1. **Adverse event (AE):** Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. The event can be unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be to the medicinal product [1].
2. **Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect:** An adverse drug reaction is defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function [2].
3. **Antimicrobial Agent:** An antimicrobial agent is defined as a natural or synthetic substance that kills or inhibits the growth of micro-organisms such as bacteria, fungi, and algae [3].
4. **Antimicrobial classification:** Drugs can be classified according to their chemical composition and type of therapeutic effect. Antimicrobials are a distinct class used to treat various infections [4].
5. **Antimicrobial Resistance (AMR):** Antimicrobial resistance occurs when microorganisms such as bacteria, viruses, fungi, and parasites change in ways that render the medications used to cure the infections they cause ineffective [5].
6. **Drug safety:** It is the main aspect of medicinal therapy that can play a major role in deciding which drug should be given to a patient [6].
7. **Drug:** Any substance, other than food, that is used to prevent, diagnose, treat, or relieve symptoms of a disease or abnormal condition. It also refers to a substance



that alters mood or body function, or that can be habit-forming or addictive, especially a narcotic [7].

8. **Fixed-Dose Combination:** Fixed-dose combination drugs are defined as ‘a combination of two or more actives in a fixed ratio of doses. This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as a single entity product given concurrently or as a finished pharmaceutical product’ [8].
9. **Healthcare Professional (HCP):** For the purposes of reporting suspected adverse drug reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses, and coroners [1].
10. **International Nonproprietary Names (INN):** International Non-proprietary Names (INN) facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary name is also known as a generic name [9].
11. **Medication error (ME):** A medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient [1].
12. **Molecule:** The specific substance holding therapeutic effect for which the formulation has been developed to attain.
13. **National pharmacovigilance centre:** A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyze and give advice on all information related to drug safety [2].
14. **Presentations:** The number of ways a drug may be available in the market. They may be in the various physical forms (tablet, syrup, inhaler, etc.) or the dosage

strength. Most of the time, the presentations are developed as a result of clinical trial result confirming dosages that have been already proven and found acceptable

15. **Pharmacoepidemiology (PE):** The study of the use and effects of drugs in large numbers of people by applying epidemiological methods to studies of the clinical use of drugs in populations [10].
16. **Pharmacovigilance (PV):** According to the World Health Organization, pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems” [2].
17. **Post-authorisation safety studies (PASS):** These studies are carried out after a medicine has been authorized to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures [1].
18. **Rational Drugs:** In 1985, the Conference of Experts on the Rational Use of Drugs convened by WHO defined rational drugs as follows:  
Rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community’ [11].
19. **Risk management system (RMS):** A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions [1].
20. **Serious adverse drug reaction (SADR):** An adverse reaction that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [1].

## References

1. EMA. *Post-authorisation safety studies (PASS)*. 2012; Available from: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-0>.
2. World Health Organisation. *Pharmacovigilance*. 2002; Available from: [https://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/pharmvigi/en/](https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/).
3. Burnett-Boothroyd, S.C. and B.J. McCarthy, *Antimicrobial treatments of textiles for hygiene and infection control applications: an industrial perspective*, in *Textiles for Hygiene and Infection Control*. 2011. p. 196-209.
4. Moore, D., *Antibiotic Classification & Mechanism*. Retrieved August, 2015. **24**.
5. World Health Organisation. *Antimicrobial resistance*. 2017; Available from: <https://www.who.int/antimicrobial-resistance/en/>.
6. Alshammari, T.M., *Drug safety: The concept, inception and its importance in patients' health*. Saudi Pharm J, 2016. **24**(4): p. 405-12.
7. NIH. *NCI Dictionary of Cancer Terms*. NCI Dictionaries Available from: <https://www.cancer.gov/publications/dictionaries/cancer-terms?expand=D>.
8. World Health Organisation. *Guidelines for Registration of Fixed-dose Combination Medicinal Products*. WHO Technical Report Series 2005; Available from: <http://apps.who.int/medicinedocs/en/m/abstract/Js19979en/>.
9. World Health Organisation. *International Nonproprietary Names*. 2019 [22 September 2019]; Available from: <https://www.who.int/medicines/services/inn/en/>.
10. Montastruc, J.L., et al., [*Pharmacoepidemiology: definition, methods and applications*]. Bull Acad Natl Med, 2015. **199**(2-3): p. 263-73; discussion 273.
11. World Health Organisation. *Promoting rational use of medicines: core components*. 2002; Available from: <https://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf>.

# Chapter 1 : Introduction

To understand the dynamics of the medicines market of any country, it is vital to study both the products offered (i.e., authorized for marketing) and the available drug utilization data in different steps of the therapeutic chain of medicines (value chain).

Health is a basic human right, as stated in the article 12 of ICESCR “the States Parties to the present Covenant recognize the right of everyone to the enjoyment of the highest attainable standard of physical and mental health” [1], and the availability of medicines is a key component in helping to ensure this right.

The availability of medicines to patients is primarily dependent on what is authorized or registered for marketing by the concerned drug regulatory authority (DRA) for a particular territory. The registration of drugs, also known as product licensing or marketing authorisation is the first step in the therapeutic chain followed by distribution, marketing, prescription, dispensing, and consumption [2].

The status of a patient’s health could be at risk if the prescribed medicines are not available for consumption. So, there is a continuous need for drug development for both old and new maladies, but developing a drug is a long, complicated, and expensive process with uncertainty about its efficacy and safety in both short and long terms [3]. Despite these difficulties, the medicines discovered and approved at a Global scale skyrocketed over the last 30 years, a period also known as the Golden Age of pharmacology.

Interestingly, amidst this growth of the pharmaceutical market, in 1980, Lunde already said that “there has been no proof of greater public health benefits with an infinite number of drugs” [4] and almost four decades later it is still relevant to the pharmaceutical markets in both developing and the developed countries.

Although nearly two billion people, majority residing in low or middle income countries lack access to essential medicines [5], the universal access to medicine cannot be

guaranteed by increasing the number of molecules in the medicine's market [6], and at the same time, too many registered medicines complicate the role of the prescriber, dispenser, consumer, and the whole supply chain in some cases. 'Access' is defined as "the reliable and consistent availability of appropriate essential, quality medicines at health facilities, the rational prescribing and dispensing of such medicines, and ensuring that they are affordable" [7].

A balance between healthcare needs and the insatiable desire to market new products, in order to increase the profits of the manufacturers, is necessary to protect the healthcare system and the citizens. One of the tools to attain this balance is regulation.

In fact, the robustness of a drug regulatory system is an indication of the policies, laws, and procedures set in place to make medicines available in the market [8]. The National Medicines Policy of a given country is the framework to try to ensure the authorization of high quality medicines with a proven risk/benefit relationship, which can be prescribed, dispensed, sold, and used under strict and well-defined conditions, taking into account the public health interests.

Additionally, the same National Medicines Policy can allow additional protection measures defined by the Drug Regulatory Authority (DRA). For example, after the dossier submission for registration when the quality, safety, efficacy, and the proposed price are being assessed, the authorities should consider adding the 'needs' clause to its checklist as Norway had included it in the legislation governing the registration of medicines [9]. Considering the need of particular medication in the market will help control the unnecessary expansion of the market width and thus limit the unnecessary exposure to patients in particular and the public in general.

Thus, the medicines market of a country is the result of adding the new authorized products to those already existing (sometimes, since many years ago, even before the

consideration of the evidence-based medicine principles). On the other hand, DRAs can withdraw a given product from the market, if there is a change of its risk/benefit relationship, either after the discovery of previously unknown adverse drug reactions (ADRs) or the reassessment of its alleged benefits.

So, the medicines market of a country is something dynamic, and, in several countries, resubmission of the dossiers for any medicinal product is compulsory five or 10 years after the first submission. Notwithstanding this, in other countries, once approved, manufacturers are never required to resubmit the dossier for evaluation. This explains why many old-fashioned or even irrational products can be found in specific countries nowadays.

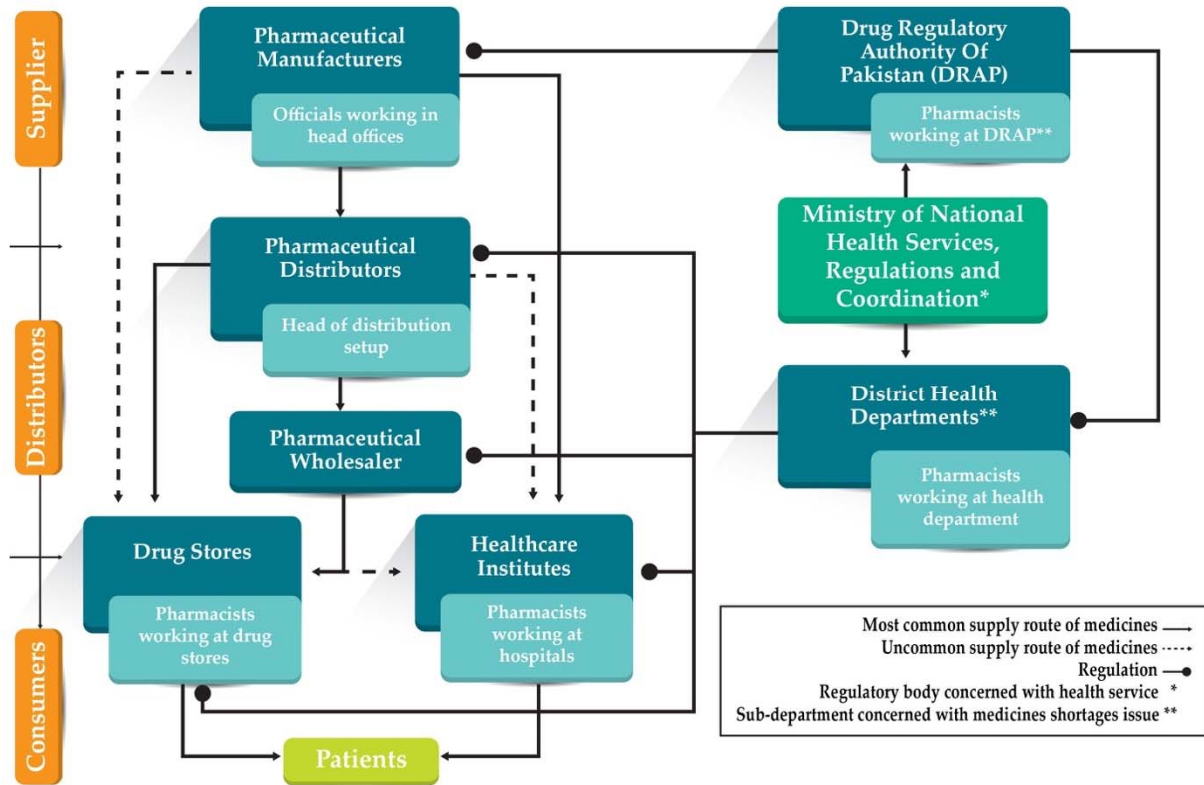
## **1.1 Different medicines markets**

Along with high disease burden [10] medicines market in the developing countries is mostly out of pocket with partial or limited insurance coverage, especially for those at lower income levels [11], which has multiple implications on the access of medicines. In addition to the formal medicines market (including those products registered with the DRA), there are the so-called informal markets, which help to determine the many ways a pharmaceutical industry operates in a country. Both formal and informal markets work in tandem; what is not present in the formal market becomes an important item for availability in an informal market [12].

Along with the regular allopathic pharmaceutical market offering branded generics and innovator brands, Pakistan has multiple alternative medicine schools of thought, and these include Unani, Hakimi, Herbal, Homeopathic, Tibb, Chinese, etc. and sometimes these medicines are sold in pharmacies as well. An overview of the pharmaceutical supply chain in Pakistan is explained in Figure 1, which gives a reasonable idea about the key stakeholders involved and various levels.



Figure 1: Tiers of the pharmaceutical supply chain in Pakistan and key stakeholders.



(adapted from [13])

For the first time, DRAP has started the assessment, enlistment, licensing, and registration of alternative medicines such as Ayurvedic, Chinese, Unani, Homeopathy, and of nutritional products and food supplements for human beings and animals with almost 22,000 applications submitted during the last five years [14]. The exact impact of this regulatory activity would have to be assessed for multiple outcomes of interest.

The number of pharmaceutical products being marketed and available for consumption at a certain time may not be equivalent to the actual number of registered products in the country. The other potential challenge is the substantial presence of substandard, spurious, falsely labeled, falsified, or counterfeit medical products [15].

## **1.2 Harmonised Regulatory Actions**

The harmonisation of regulatory processes while registering a new chemical entity with a common technical document (CTD) used by many regulatory authorities [16] has undoubtedly eased and simplified the process. New chemical entities are rather quickly registered in the developing countries based on their prior registration status with another stringent regulatory authority, namely, FDA, EMA, or PMDA.

The idea that a good scientific evidence should trigger each medical assertion, a medical decision, and a possible medical prescription is almost five decades old [17]. At the time of drug registration, many questions remain unanswered, and many subsequent **regulatory decisions** are increasingly dependent on a multidimensional data generated through evidence based medicine (EBM) and real world evidence (RWE).

Real world evidence is the actual analysis of real world data from electronic health records (EHR), disease and product registries, and data from insurance and wearables, including monitoring devices [18]. The 21st Century Cures Act defines RWE as evidence derived from “data regarding the usage, or potential benefits or risks, of a drug derived

from sources other than randomized clinical trials” [19] which offers an exceptional understanding of the safety and effectiveness data from a patient’s daily life [18].

### **1.3 Globalization**

**Globalization** of various regulatory decisions has been observed over the last few years as was seen with the withdrawal of Phenylpropanolamine from Latin American countries [20], but the drug was still available in India and listed in the 2006 edition of the Current Index of Medical Specialties (CIMS) drug database as a combination with atorvastatin, paracetamol, and nicotinic acid cetirizine [21].

In 2018, when an impurity, N-nitrosodimethylamine (NDMA) was detected in the valsartan active substance [22], it triggered a worldwide recall with 24 countries, including Pakistan as one of the first developing country recalled more than 2300 batches immediately [23]. Most recently, the European Medicines Agency (EMA) announced to start a review of ranitidine medicines after tests showed the presence of NDMA in some products [24].

Many developing countries continue to consume medicines that were discontinued or withdrawn for safety and efficacy reasons from other countries [25]. However, since the developed countries have relatively better information on a drug’s benefits, risks, and usage, the regulatory decisions are taken promptly, which may not be the case for most of the developing countries [26].

Citing the small increase in the bladder cancer, the French regulatory authority withdrew the marketing authorisation of pioglitazone in 2011 [27], which was not banned from the Indian markets until June 2013 and the drug technical advisory board of India later revoked the ban citing insufficient evidence [28].

## 1.4 Added Value of Medicines

There is more tendency to assess the added value of new medicines to address the limited new paediatric drug approvals in the EU a paediatric regulation was introduced in the year 2007. It required all pharmaceutical companies to submit a paediatric investigation plan for every new medicine, and the regulation helped generate more subject relevant data and approved medicines for paediatric use [29].

The same concern has been raised for women who have been largely excluded in clinical trials. It is now widely accepted that gender differences may have an effect on how a drug is metabolized in the body and its side effects. Since most trials in the past have recruited males, the effect of these medicines on women is largely unknown [30].

FDA's accelerated application (AA) and EMA's conditional marketing authorization (CMA) regulations were introduced to improve drug access for diseases that are life-threatening illnesses, although the magnitude of them is not overwhelming [31]. EMA's adaptive licensing route is another example of an adaptive regulatory initiative to provide fast access to innovative medicines.

Availability of essential medicines to patients is also dependent on their prices, and regulatory authorities in some countries have introduced special laws providing for the mandatory re-registration of prices for all essential drug lists and failing to do so will de-register those products [32]. The main objective of such interventions is to improve the patient affordability and access to these essential medicines, as elevated median price ratio (MPR) for these medicines have also been observed in other middle income countries [33].

## 1.5 Prescription & Dispensing

The decision on what to prescribe is quite complex and dependent on multiple factors, including the prescriber's academic training, cultural beliefs, past experience, access to independently prepared relevant information, promotional campaigns by the pharmaceutical industry, and the pharmaceutical market width [34]. Also, a prescription mentioning a brand (originator), generic (drug's INN), or a generic brand could influence the way the prescription is dispensed. Patients are more likely to identify their medication by brand name rather than the generic name [35].

Another stimulus to prescription behaviour is known to be the introduction of new products (possibly in the same class), which are mostly more expensive, causing expenditure growth [36, 37]. An out-of-pocket market for healthcare interestingly molds the prescribing and dispensing behaviors. In the case of lower income groups, for instance, who could only visit the public hospitals, the HCPs are often restricted to prescribe medicines available in the hospital pharmacy with an additional evaluation on cost vs. benefit for these poor patients, leading to the prescription of only what's absolutely necessary.

Theoretically, clinical guidelines, drug bulletins (international if not national) along continuing medical education and publications in medical journals should be the basis of most therapeutic decisions [38], but the prescribing behaviours in Pakistan show the average number of prescribed drugs per prescription is around 3.5 [39]. Drugs per prescription are as up to 4.5 in private clinic prescriptions [40], whereas the average number of drugs prescribed per patient in LMICs is two to three [39].

Interestingly, the patients prescribed with more than three drugs per prescription had longer stay in the hospital and were more likely to experience the prescribing errors [41].

Another interesting concept to understand the prescribing practices in developing countries is the emotional influence, which could be both positive and negative, depending on a multitude of factors [38].

The irrational prescription percentage for antibiotics was found very high in both public and private sector hospitals for almost all age groups, and for some of the 'Watch' group antibiotics, the prescribing frequency was more than 80% showing high resistance rates [42]. The choice of an antibiotic medicine may be for prophylactic, empirical, or therapeutic reasons is dangerously high for pediatric patients, and risks are further elevated when there is more than one antibiotic prescribed in an intensive care unit [43].

The use of irrational medications, including antibiotics, is also prevalent amongst the students [44], especially if they are from urban areas and studying health sciences subjects. Antibiotics are one of the most common choices of self-prescribed drugs during the common cold or flu [45].

Due to the multifactorial nature of a health care system, irrational prescribing and consumption behaviour could be induced by personal, institutional, and community factors [46].

**The dispensing** of any drug, with either authorized or unauthorized prescription, would depend on what the pharmaceutical market has on offer. The same applies in the case of self-medication, where the access of consumers to a certain medication is dependent on its availability in the market.

It is a common observation in developing countries that medicines are dispensed with or without prescription and by both registered and unregistered health care practitioners. Apart from this, the dispensing person could be a friend, family, or relative, which increases the possibility of sharing unnecessary medicine.

## **1.6 Rationalizing antibiotic usage through protocols based on standard Guidelines**

Irrational use of antibiotics can be reduced significantly by adopting standard clinical guidelines and protocols [47]. Limiting unnecessary exposure to these otherwise beneficial medicines, if used rationally, can help avoid unwanted adverse drug reactions, the unnecessary workload at a healthcare setting, and an un-justified economic burden for the patients. However, the choice of a certain guideline should be based on the specific needs of the population in question.

The need for the continuous pursuit of regulatory controls to curb the overuse of antimicrobials is demonstrated by the Chilean case where following the regulatory measures instituted in 1999 showed a sharp decline in the antibiotic consumption trends [48], but with insufficient reinforcement, within three years the consumption levels went up again [49]

Absence of national antibiotic policy, relevant clinical guidelines, irrational use (either self or prescribed), and the emergence of antibiotic resistance organisms are a dangerous recipe for antibiotic resistance [42, 45, 47].

## **1.7 Use of Medicines**

In the words of "Alexandrian physician Herophilus 300 B.C" about rational drug use, "Medicines are nothing in themselves but are the very hands of God if employed with reason and prudence"[50]. In 1985 the World Health Organization defined that "Rational use of drugs, requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"[51].



This criteria for rational use of drugs can only be fulfilled when a set of five appropriates, including indication, drug, patient, information (on indication & drug), and monitoring, are considered while making any therapeutic decision [52]. Any of these missing or not well-understood components could lead to the irrational use of medicines.

Among the twelve core interventions suggested to the countries by WHO to promote more rational use of medicines, at least four talks about the regulations. These include mandating a multidisciplinary national body to coordinate medicine use policies, continued medical education (CME) as a licensure requirement, supervision, audit & feedback, and appropriate and enforced regulation by the respective regulatory authority. It also emphasizes the use of essential medicines list and allocated resources to improve the access and management of these essential medicines across the country [53].

In developing countries, where there are fewer checks and balances, and the regulatory systems are not well-synchronized, there is a higher risk of irrational prescribing behaviour in various forms. Developing countries are also found to be fast becoming hubs of poly-pharmacy and antimicrobial resistance; trends that are highly dangerous if not addressed appropriately [8, 52].

### 1.7.1 Irrational Use

Irrational use of medicines continues to be an important problem in developing nations as it is associated with preventable adverse effects, and, in the case of antimicrobials, it is associated with another worrying phenomenon: antimicrobial resistance. The interesting factor in the case of antibiotics is that their use is influenced by many determinants such as social, demographic, economic, climatic, educational, cultural, and healthcare models [54, 55].

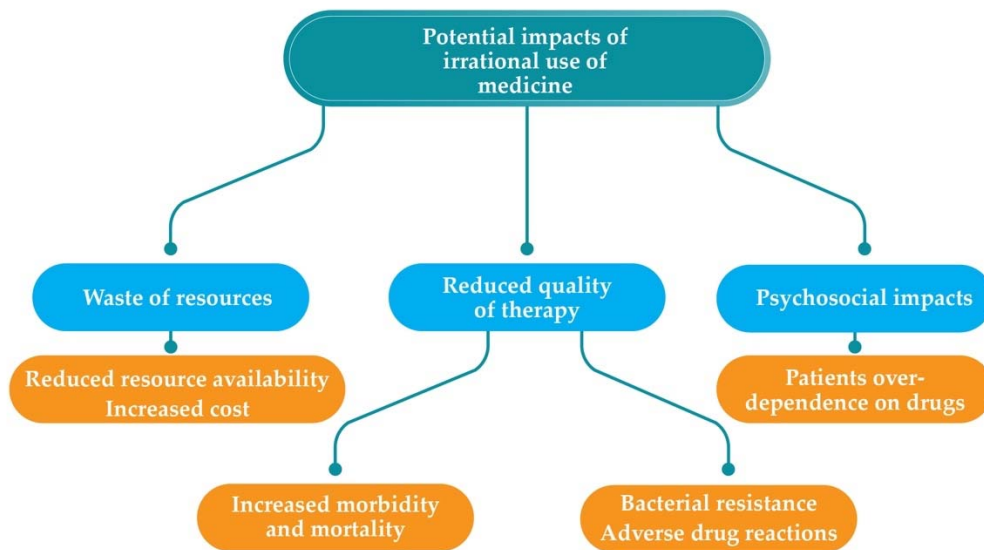
The advertising of pharmaceutical products in Pakistan is not fully compliant with the guidelines for ethical advertisements written in Drugs Act, 1976 [56] and physicians'

reliance on the updated information through these advertisements influence the prescribing behaviours [57] that could result in reduced quality of prescriptions [58]. Drug information, which is producer or marketing authorization holder independent and drug utilization statistics, can help improve the rational use of medicines [9].

The drug advertisements could also encourage unnecessary medical advice seeking behavior, and pressurize the physicians for unnecessary medical prescriptions [59].

The private sector use of antibiotics as a fixed dose combination was another lethal combination noticed in multiple developing countries from the Latin American region, where up to 91% of these combinations were either unsafe or had insufficient evidence on efficacy[60]. Irrational prescribing behaviours indicate missing elements or flaws in the overall system that may require attention or change. Some of the potential impacts of irrational use of medicines are summarized in Figure 2

Figure 2: Possible implications of the irrational use of medicines.



adapted from [8]

## **1.8 Cleaning the Medicines Market**

Despite limited regulation enforcement in developing countries, there have been revisions on what is marketed, in order to "clean" the market. Bangladesh introduced a production ban on nearly 1700 drugs affecting 117 active ingredients in an attempt to clean the medicines market from non-essential or harmful medicines [61]. Similarly, in a major clean up on the irrational fixed dose combinations, 344 medicines were banned from the Indian medicines market [62].

Pakistan adopted the concept of essential medicines (EM), which advocates "that the use of a limited number of carefully selected medicines based on agreed clinical guidelines leads to a better supply of medicines, to more rational prescribing and to lower costs"[63]. Inspired by the WHO Model list of essential medicines (WEML), which was first introduced in 1977[53], Pakistan published its first national essential medicines list (NEML) in 1994 [64], and the most recent version was published in 2018 [65]. In the absence of reliable or limited (where available) local data on disease prevalence, drug utilization, adverse drug reactions, etc. the significance of NEML is undermined.

It would be interesting to see the extent of use of this NEML by the prescribers at different points of health care across the country as a small sample study showed limited knowledge amongst medical practitioners resulting in the limited use in the written prescriptions [66].

## **1.9 Fixed Dose Combinations**

One category of medicines susceptible to be "pruned" are FDCs, as traditionally, these combinations have been the solution for many small companies to introduce products in the market without the need of an extensive research and development staff, by just adding a component to an innovative product.

The use of an FDC strategy for high risk cardiovascular disease (CVD) patients has shown better medication adherence leading to a small but significant improvement in some clinical outcomes [67] specially among elderly hypertensive patients [68]. More recently, a new treatment alternative for secondary prevention of CVD has been emerging named 'Polypill' with at least three more drugs (Aspirin, Statin, Blood pressure lowering agent) combined together in a tablet or a capsule [69, 70]. The concept was initially proposed as a six drug combination in 2003, suggesting that CVD could be reduced by eighty percent [71].

With no significant assessment of the long term clinical outcome available, the major argument to support its usage is mainly adherence to the treatment while there is a limitation in the titration of doses and the unknown impact of multi drug tolerance[70].

The last decade has seen the emergence of many of these polypills with 3 or more drugs in a combination including Aspirin, Statin, and multiple Blood lowering agents.

Examples like these continue to form the basis and justification for manufacturers in developing countries to create different non-recommended irrational combinations. Also, in developing countries, the prescribers are priced sensitive and prefer lower priced drugs for their patients [72], making FDCs an easy choice. Creating fixed dose combinations following a quick market survey to understand the competition and scope seems to be a straight forward business decision for manufacturers [73], especially when there is a possibility to register in a quick time. A large number of irrational anti-diabetic [74] and psychotropic [75] medications continue to be present in the Indian markets despite a major cleanup of 344 FDCs in 2016 [76].

FDCs in developing countries continue to be available in a substantially high number [77, 78] and in all kinds of formulations with ingredients from multiple ATC groups put together [79], further elevating potentially unknown and dangerous types of risks. A high

number of fixed-dose combinations in the country reflects a poorly regulated pharmaceutical market [80]. Any experimental recommendation without careful and critical clinical evaluation should not be adopted for combination therapies.

## **1.10 Summary**

While premarketing assessment to register a product is very important, it is only of much relevance if the efficacy and, especially, the safety of drugs are to be assured. Pharmacovigilance with quality control testing, adverse drug reaction monitoring, and re-evaluation of registered products, should also be the priority areas in drug regulation. Analysing the medicines market should be the first step for a country to try to make the medicine's consumption more rational (of course, it is not the only action, but should be the first):

- a. to increase patient safety by avoiding unnecessary or avoidable adverse effects,
- b. by reducing antimicrobial resistance due to inappropriate use of AM, and
- c. to improve the quality of health care in the country which is associated with:
  - i. improvement in the quality of life of Pakistan people and
  - ii. the economic development of the country.

## 1.11 Objectives of the study

The overall objective of this study was to show that a lower-middle-income country like Pakistan can begin to improve the rational use of medicines by understanding its medicine's market

The specific study objectives were as follows

1. To describe the availability and consumption of registered antimicrobial medicines (ATC group J01) with a focus on 'Watch' group antimicrobials.
2. To investigate the utilization trends for the two highest-selling antimicrobial classes (cephalosporins & fluoroquinolones) for five years (April 2014 to March 2019).
3. To estimate the availability of registered fixed-dose combinations focusing on irrational combinations withdrawn in other countries.

**Chapter 1** presents an overall introduction about the concept of medicines market analysis for a country? How medical prescriptions are dependent on what is available in the market, globalization of regulatory decisions across the world. It further discusses the concept and rationale of cleaning the market with medicines like fixed-dose combinations, highlighting the irrational use of antibiotics, and explaining how analyzing the medicines market could to be the first step to promote the rational use of medicines.

**Chapter 2** is a general view of the **methodology used for this thesis**. Pakistan lacks the official central repository of registered medicines with data on prescription from all sources of healthcare delivery, such as primary care, private and public healthcare institutions, pharmacies, rural care clinics, prescriptions given out by lady health workers, etc. To address this and answer our research question, we used national sales data from IQVIA Pakistan formerly (IMS, Pakistan). Chapter 2 will describe the choice of data and reasons

**Chapter 3** answers the question: **What is the market width for antimicrobials in Pakistan focusing on *Antibacterials for systemic use* (ATC code J01), which is a therapeutic subgroup of the Anatomical Therapeutic Chemical Classification System, with an in-depth analysis of “Watch” group?** WHO recommends the countries to develop and implement the essential medicines lists. The list includes the antibiotics categorized as access, watch, and reserve and mentions how to be used as first and second choices for the empirical treatment for the common or severe clinical symptoms. It is important to analyze how many of these antibiotics are presently available in Pakistan to understand the market width and possible prescription behaviors. Chapter 2 describe the antibiotics (ATC J01) medicine offerings in Pakistan, with a particular reference to drugs that have been categorized as “Watch” active ingredients.

**Chapter 4** deals with the question: **How the antibiotic consumption for the two most sold antimicrobial classes (Cephalosporins & Fluoroquinolones) have changed in Pakistan during the period of five years (April 2014 – March 2019)?**

One main barrier to ineffective antimicrobial response is antimicrobial resistance, which is high among counties with high levels of antibiotic consumption. Both cephalosporin and fluoroquinolones are broad-spectrum antibiotics that treat a range of infections. Chapter 3 investigates the trends in consumption of cephalosporins and fluoroquinolones antibiotics in Pakistan for five years .

After understanding the antimicrobial market, the presence of ‘Watch’ group antibiotics and the consumption of the two most selling antimicrobial classes (J01D & J01M) **Chapter 5** assesses the question: **What fixed-dose combinations are registered and available in the country focusing the ones that have been discontinued in other countries but are still available in Pakistan. Since 1950’s fixed-dose combination has been pitched as a therapy that simplifies the treatment regimens, it improves adherence, thus avoiding**

treatment failures with the rationale of better hypertensive management when two pharmacological classes are combined. Many irrational FDCs have been introduced in the developing countries, causing the unnecessary **burden** of adverse drug reactions, especially among high-risk patient groups. It is essential to know a different kind of combinations are available in the market as this information is relevant to inform policymakers on the actual use and access to fixed-dose combinations that have been banned in other markets. Chapter 4 describes the total medicines offering in Pakistan as a fixed-dose combination and consumption of those that are already withdrawn from other countries due to safety reasons.

In Chapter 6, the **general discussion**, all findings from the previous chapters are summarized and discussed to address the overall research question of the thesis. The chapter also includes a section on policy implications of the findings, limitations, and considerations, while Chapter 7 lists the final conclusions.



## 1.12 References

1. UN. *International Covenant on Economic, Social and Cultural Rights*. 1966; Available from: <https://www.ohchr.org/EN/ProfessionalInterest/Pages/CESCR.aspx>.
2. Figueras, A., et al., *Health needs, drug registration and control in less developed countries--the Peruvian case*. *Pharmacoepidemiol Drug Saf*, 2002. **11**(1): p. 63-4.
3. Neuroscience, I.o.M.F.o., N.S. Disorders, and S.M.P. Norris, *Improving and Accelerating Therapeutic Development for Nervous System Disorders: Workshop Summary*. 2014: National Academies Press.
4. Lunde, P.K.M., 'Drug and product selection-an essential part of the therapeutic benefit risk ratio strategy? Drug-induced Sufferings, *Excerpta Medica*, Amsterdam, 1980: p. 129-36.
5. World Health Organization, *World health statistics 2016: monitoring health for the SDGs sustainable development goals*. 2016: World Health Organization.
6. Babar, Z.-U.-D., et al., *The Pharmaceutical Industry, Intellectual Property Rights and Access to Medicines in Pakistan*, in *The New Political Economy of Pharmaceuticals: Production, Innovation and TRIPS in the Global South*, H. Löfgren and O.D. Williams, Editors. 2013, Palgrave Macmillan UK: London. p. 167-184.
7. World Health Organization, *Addressing the global shortage of, and access to, medicines and vaccines Report by the Director-General BACKGROUND*. Vol. EB142/13. World Health Assembly, 2018.
8. Ofori-Asenso, R. and A.A. Agyeman, *Irrational Use of Medicines-A Summary of Key Concepts*. *Pharmacy (Basel)*, 2016. **4**(4).
9. Andrew, M., B. Joldal, and G. Tomson, *Norway's national drug policy. Its evolution and lessons for the future*. *Dev Dialogue*, 1995. **1**: p. 27-53.
10. World Health Organization, *WHO global coordination mechanism on the prevention and control of noncommunicable diseases: final report: WHO GCM*. 2018, World Health Organization.
11. Danzon, P., *Biopharmaceutical and Medical Equipment Industries, Economics of*, in *Encyclopedia of Health Economics*, A.J. Culyer, Editor. 2014.
12. Kohler, J.C., et al., *An examination of pharmaceutical systems in severely disrupted countries*. *BMC Int Health Hum Rights*, 2012. **12**: p. 34.
13. Atif, M., et al., *Medicines shortages in Pakistan: a qualitative study to explore current situation, reasons and possible solutions to overcome the barriers*. *BMJ Open*, 2019. **9**(9): p. e027028.
14. DARP. *Health and OTC Products Division 2019* 15 September 2019]; Available from: <http://dra.gov.pk/Home/HOTC>.

15. Ozawa, S., et al., *Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis*. JAMA Network Open, 2018. **1**(4): p. e181662-e181662.
16. Molzon, J., *The Common Technical Document: the changing face of the New Drug Application*. Nature Reviews Drug Discovery, 2003. **2**(1): p. 71-74.
17. Cochrane, A., *Effectiveness and efficiency: Random reflections on health services*. 1972.
18. Xuanyan, X. *Why is the Pharma Industry Buzzing About Real-World Evidence?* 2019; Available from: <https://pharma.elsevier.com/pharma-rd/why-is-the-pharma-industry-buzzing-about-real-world-evidence/>.
19. *21st Century Cures Act*, in H.R.34 2016, 114th Congress.
20. Figueras, A. and J.R. Laporte, *Regulatory decisions in a globalised world: the domino effect of phenylpropanolamine withdrawal in Latin America*. Drug Saf, 2002. **25**(10): p. 689-93.
21. Sreedhar, D., et al., *Fixed dose combinations: Rational or irrational*. Current science, 2008. **95**(5): p. 581-583.
22. European Medicines Agency, E., *EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity* 2018, European Medicines Agency: London.
23. Farrukh, M.J., et al., *Valsartan recall: global regulatory overview and future challenges*. Therapeutic advances in drug safety, 2019. **10**: p. 2042098618823458.
24. European Medicines Agency, E., *EMA to review ranitidine medicines following detection of NDMA*. 2019.
25. Onakpoya, I.J., C.J. Heneghan, and J.K. Aronson, *Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature*. BMC medicine, 2016. **14**(1): p. 10.
26. Kshirsagar, N., *Post-marketing safety signals: Challenges in regulatory decisions, communication & impact evaluation in developing countries*. Indian J Med Res, 2017. **146**(4): p. 445-447.
27. Wood, S. *French Regulators Suspend Pioglitazone Citing Cancer Risk*. 2011 16 September 2019]; Available from: <https://www.medscape.com/viewarticle/744345>.
28. Pai, S.A. and N.A. Kshirsagar, *Pioglitazone utilization, efficacy & safety in Indian type 2 diabetic patients: A systematic review & comparison with European Medicines Agency Assessment Report*. Indian J Med Res, 2016. **144**(5): p. 672-681.
29. Tomasi, P.A., et al., *Enabling Development of Paediatric Medicines in Europe: 10 Years of the EU Paediatric Regulation*. Pediatric Drugs, 2017. **19**(6): p. 505-513.
30. Prout, M.N. and S.S. Fish, *Participation of women in clinical trials of drug therapies: a context for the controversies*. Medscape Womens Health, 2001. **6**(5): p. 1.

31. Borrell Puy, M., et al., *1563PD Magnitude of clinical benefit in trials supporting US Food and Drug Administration (FDA) accelerated approval (AA) and European Medicines Agency (EMA) conditional marketing authorisation (CMA) and subsequent trials supporting conversion to full approval*. *Annals of Oncology*, 2018. **29**(suppl\_8): p. mdy297. 007.
32. Tyupa, V. and A. Shadrin. *Prices for essential drug list medicines subject to mandatory re-registration in Russia*. 2019; Available from: <https://www.lexology.com/library/detail.aspx?g=9e169c95-72c9-405e-aa1a-0d2ecd2b127a>.
33. Ahmad, N.S. and F. Islahudin, *Affordability of essential medicine prices in Malaysia's private health sector. Patient preference and adherence*, 2018. **12**: p. 1231.
34. Diogene, E. and A. Figueras, *What public policies have been more effective in promoting rational prescription of drugs?* *J Epidemiol Community Health*, 2011. **65**(5): p. 387-8.
35. Tranchard, F., et al., *Drug identification by the patient: Perception of patients, physicians and pharmacists*. *Therapies*, 2019.
36. Morgan, S.G., et al., *"Breakthrough" drugs and growth in expenditure on prescription drugs in Canada*. *BMJ*, 2005. **331**(7520): p. 815-816.
37. Canadian Institute for Health Information. *Drug expenditures in Canada 1985–2004*. 2005.
38. Figueras, A., *The use of drugs is not as rational as we believe... but it can't be! The emotional roots of prescribing*. *Eur J Clin Pharmacol*, 2011. **67**(5): p. 433-5.
39. World Health Organisation. *The world medicines situation*. 2004; 2nd edition:[Available from: [https://apps.who.int/iris/bitstream/handle/10665/68735/WHO\\_EDM\\_PAR\\_2004.5.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/68735/WHO_EDM_PAR_2004.5.pdf?sequence=1)].
40. Atif, M., et al., *Evaluation of prescription errors and prescribing indicators in the private practices in Bahawalpur, Pakistan*. *Journal of the Chinese Medical Association*, 2018. **81**(5): p. 444-449.
41. Iftikhar, S., et al., *Antibiotic prescribing practices and errors among hospitalized pediatric patients suffering from acute respiratory tract infections: a multicenter, cross-sectional study in Pakistan*. *Medicina*, 2019. **55**(2): p. 44.
42. Baig, M.T., et al., *Irrational antibiotic prescribing practice among children in critical care of tertiary hospitals*. *Pak J Pharm Sci*, 2017. **30**(4(Suppl.)): p. 1483-1489.
43. Abbas, Q., et al., *Evaluation of antibiotic use in Pediatric Intensive Care Unit of a developing country*. *Indian J Crit Care Med*, 2016. **20**(5): p. 291-4.
44. Rehman, M.U., et al., *Trend Of Irrational Medication Among The Students Of Department Of Pharmacy Abbottabad University Of Science And Technology In Common Cold And Flu*. *J Ayub Med Coll Abbottabad*, 2017. **29**(1): p. 87-89.

45. Saleem, Z., et al., *Antibiotic Self-Prescribing Trends, Experiences and Attitudes in Upper Respiratory Tract Infection among Pharmacy and Non-Pharmacy Students: A Study from Lahore*. PLoS One, 2016. **11**(2): p. e0149929.
46. Mohamadloo, A., et al., *The Main Factors of Induced Demand for Medicine Prescription: A Qualitative Study*. Iran J Pharm Res, 2019. **18**(1): p. 479-487.
47. Nausheen, S., R. Hammad, and A. Khan, *Rational use of antibiotics--a quality improvement initiative in hospital setting*. J Pak Med Assoc, 2013. **63**(1): p. 60-4.
48. Bavestrello, L. and A. Cabello. *How Chile tackled overuse of antimicrobials*. Essential Drugs Monitor No. 028-029 (2000) 2000 06 October 2019].
49. Bavestrello, F.L. and M.A. Cabello, *[Community antibiotic consumption in Chile, 2000-2008]*. Rev Chilena Infectol, 2011. **28**(2): p. 107-12.
50. Shivhare, S.C., et al., *Drugs Hazards and Rational Use of Drugs: A Review*. Journal of Chemical and Pharmaceutical Research, 2010. **2**(1): p. 106-112.
51. World Health Organization. *The rational use of drugs: report of the Conference of Experts. Nairobi. November 25–29, . 1985*.
52. World Health Organisation. *Problems of Irrational Drug Use, Session Guide*. 2000 13 September 2019]; Available from: <http://archives.who.int/PRDUC2004/RDUUCD/Session Guides/problems of irrational drug use.htm>.
53. World Health Organisation. *The Selection of Essential Medicines WHO Policy Perspectives on Medicines, No. 4 2002 05 October 2019]; Available from: https://apps.who.int/medicinedocs/en/d/Js2296e/*.
54. Renwick, M.J., D.M. Brogan, and E. Mossialos, *A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics*. J Antibiot (Tokyo), 2016. **69**(2): p. 73-88.
55. Tamhankar, A.J., S.S. Karnik, and C. Stalsby Lundborg, *Determinants of Antibiotic Consumption - Development of a Model using Partial Least Squares Regression based on Data from India*. Sci Rep, 2018. **8**(1): p. 6421.
56. Vakani, F., K. Naqvi, and A. Amin, *Content audit of drug advertisements in Pakistan*. Indian Journal of Medical Ethics, 2011. **VIII**(3).
57. Ahmad, S.R. and Z.A. Bhutta, *A survey of paediatric prescribing and dispensing in Karachi*. J Pak Med Assoc, 1990. **40**(6): p. 126-30.
58. Spurling, G.K., et al., *Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review*. PLoS medicine, 2010. **7**(10): p. e1000352.
59. Schommer, J.C., R.L. Singh, and R.A. Hansen, *Distinguishing characteristics of patients who seek more information or request a prescription in response to direct-to-consumer advertisements*. Res Social Adm Pharm, 2005. **1**(2): p. 231-50.

60. Wirtz, V.J., et al., *Use of antibacterial fixed-dose combinations in the private sector in eight Latin American Countries between 1999 and 2009*. *Tropical Medicine & International Health*, 2013. **18**(4): p. 416-425.
61. Faruque, A.A., *Problems of enforcements of regulations on pharmaceutical industry in Bangladesh*. 2014.
62. National Health Portal, N. *Complete list of 344 drugs banned by the Ministry of Health Family welfare*. 2016; Available from: [https://www.nhp.gov.in/Complete-list-of-344-drugs-banned-by-the-Ministry-of-Health-Family-welfare\\_pg](https://www.nhp.gov.in/Complete-list-of-344-drugs-banned-by-the-Ministry-of-Health-Family-welfare_pg).
63. World Health Organisation. *How to develop and implement a national drug policy*. WHO Policy Perspectives on Medicines, No. 6. 2003 [14 September 2019]; Available from: [https://apps.who.int/iris/bitstream/handle/10665/67759/WHO\\_EDM\\_2002.5.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/67759/WHO_EDM_2002.5.pdf?sequence=1).
64. World Health Organisation. *National essential drugs list of Pakistan*. 2003 [cited 15 September 2019; Available from: [https://www.who.int/selection\\_medicines/country\\_lists/pak\\_2003.pdf?ua=1](https://www.who.int/selection_medicines/country_lists/pak_2003.pdf?ua=1).
65. Drug Regulatory Authority of Pakistan, D. *Essential Medicines List*. 2018. 2018; Available from: <https://www.dra.gov.pk/Home/Download?ImageName=Final%20Design%20NEML%20OCTOBER%202018.pdf>.
66. Tahir, M. and M. Irfan, *NATIONAL ESSENTIAL MEDICINES LIST OF PAKISTAN: USE IN PRESCRIPTIONS AND AWARENESS IN MEDICAL PRACTITIONERS*. *Journal of Postgraduate Medical Institute (Peshawar-Pakistan)*, 2017. **31**(3).
67. Thom, S., et al., *Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial*. *JAMA*, 2013. **310**(9): p. 918-29.
68. Verma, A.A., et al., *Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: A population-based retrospective cohort study*. *PLoS Med*, 2018. **15**(6): p. e1002584.
69. Hedner, T., et al., *The polypill: an emerging treatment alternative for secondary prevention of cardiovascular disease*. 2016, Taylor & Francis.
70. Roy, A., N. Naik, and K. Srinath Reddy, *Strengths and Limitations of Using the Polypill in Cardiovascular Prevention*. *Curr Cardiol Rep*, 2017. **19**(5): p. 45.
71. Wald, N. and M. Law, *A strategy to reduce cardiovascular disease by more than 80%*. *BMJ*, 2003. **327**(7415): p. 586.
72. Ankush, C., et al., *A SURVEY ON DOCTOR'S EXPECTATION FROM MEDICAL REPRESENTATIVE IN KARNATAKA STATE*. *International Journal of Current Research and Review*, 2015. **7**(8): p. 75.

73. Miranda, M.R.H., et al., *Fixed-dose combinations banned in India: is it the right decision? An eye-opening review*. *Expert Opin Drug Saf*, 2019. **18**(10): p. 977-985.
74. Evans, V. and A.M. Pollock, *The proliferation of irrational metformin fixed-dose combinations in India*. *The Lancet Diabetes & Endocrinology*, 2015. **3**(2): p. 98-100.
75. Solanki, M.S. and G. Banwari, *Irrational fixed dose combinations of psychotropic drugs in India: Cause of concern*. *Indian journal of pharmacology*, 2016. **48**(4): p. 468.
76. Ministry of Health and Family Welfare, *Government of India Notification 2016*: New Delhi.
77. Poudel, A., et al., *Evaluation of the registration status of fixed-dose drug combinations in Nepal*. *Journal of Pharmaceutical Health Services Research*, 2018. **9**(1): p. 41-46.
78. CDSCO. *Fixed dose combinations approved by DCG (I) since 1961 till 22nd February 2019*. 2019; Available from:  
[https://cdsco.gov.in/openccms/openccms/system/modules/CDSCO.WEB/elements/download\\_file\\_division.jsp?num\\_id=NDEwOQ==](https://cdsco.gov.in/openccms/openccms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NDEwOQ==).
79. Auwal, F., M.N. Dahiru, and S.N. Abdu-Aguye, *Availability and rationality of fixed dose combinations available in Kaduna, Nigeria*. *Pharmacy Practice*, 2019: p. 1470-1470.
80. Castel, J.M., et al., *Multicenter study on self-medication and self-prescription in six Latin American countries*. *Clinical Pharmacology & Therapeutics*, 1997. **61**(4): p. 488-493.

## **Chapter 2 : Methodology**



Numerous methods could be used to study the medicines market through out the therapeutic chain. To understand the medicines market of Pakistan, three quantitative drug utilization studies were designed to estimate the presence and consumption of registered antimicrobials and fixed dose combinations in the country.

## **2.1 Drug Utilization Studies**

WHO defined drug utilization as the “marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences[1]. The therapeutic chain of medicines consists of multiple processes including development, regulation, which includes registration, marketing, distribution, prescription, dispensing, and their use [2] while the cycle of medicines uses has four stages including diagnosis, prescription, dispensing and patient adherence [3].

Inappropriate use of medicines can be triggered at any of the above mentioned steps or stages by single or multiple factors.

## **2.2 Type of Drug Utilization Studies**

Drug utilization studies are essential to understand the rationality as it provides extremely valuable information about the availability of medicines and their use as the study outcomes could lead to decisive policy actions.[4]. Different types of methodological approaches can be taken to design and conduct these studies, and the choice of a certain type, either quantitative or qualitative [5], would depend on systems & structures, processes, or outcomes of drug use [6].

Quantitative drug utilization studies could be useful in describing the situation at present regarding medicines use and its prescription trends[6] while qualitative data generally attempts to estimate that how appropriate[7] is the drug utilization and the reasons for a



certain prescription trend, hence the research on drug utilization can provide useful information on pattern, quality, determinants, and outcomes of medicines use [6].

### **2.3 Drug Utilization Data:**

Most of the drug utilization data is collected for administrative or commercial objectives, which are presented as units, costs, number, or volume of tablets, capsules, suspension, injectable, or doses [5]. The type of drug utilization studies performed in a country would largely depend on the type of dataset available for analysis, which varies with the health care system's structure, processes, and sophistication[6].

Due to the smaller population size and a limited number of registered pharmaceutical products, drug utilization research is more developed with the quantitative methodology in Europe compared to the US [5].

Like many other developing countries, Pakistan lacks an official central repository of registered medicines with data on prescription from all sources of healthcare delivery such as primary care, private and public healthcare institutions, pharmacies, rural care clinics, prescriptions given out by lady health workers, etc.

The drug utilization data, if and when accessible, from the drug regulatory authority, distribution network, or from health care centers with prescription and dispensing records, is scanty at best. This, however, does not account for prescription and dispensing transactions triggered by a self-treating behavior resulting in self-medication.

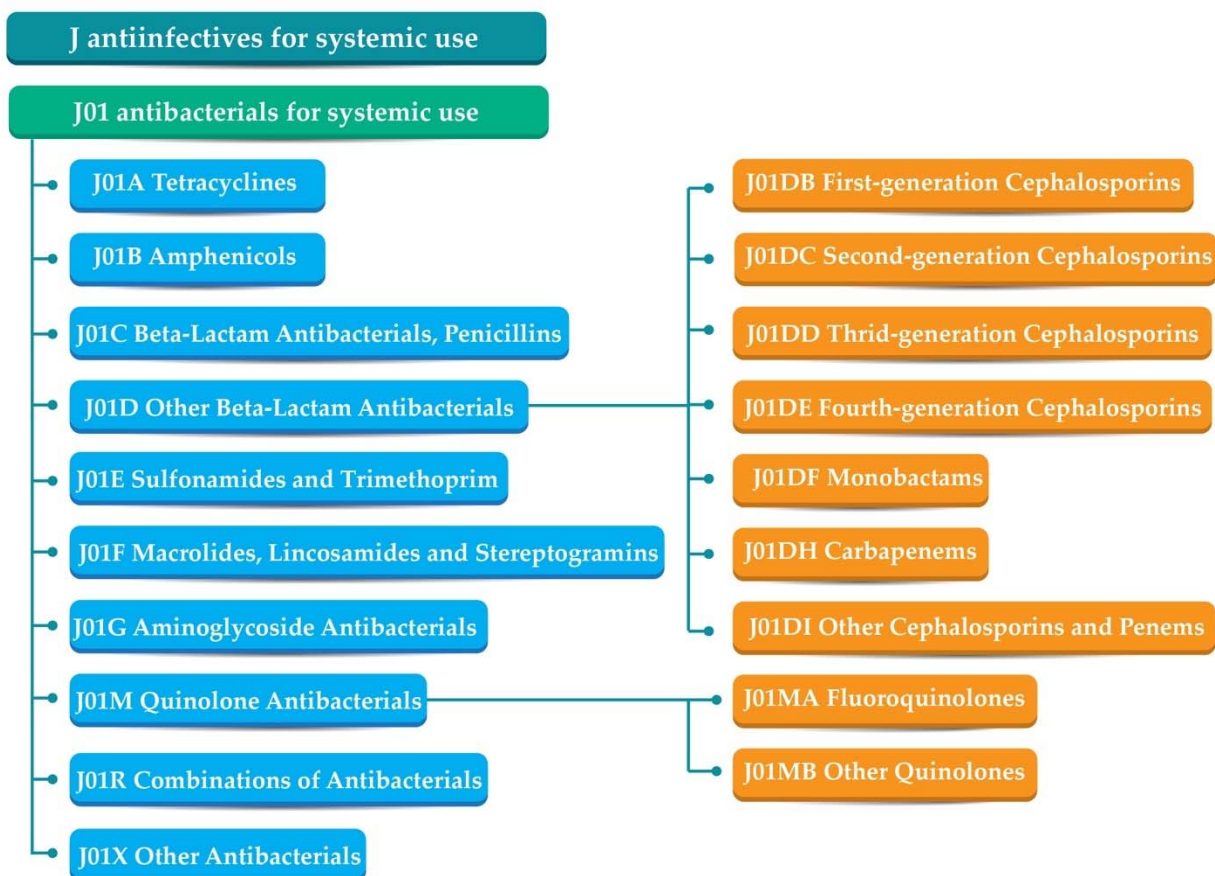
Approximately 80,000 products (single and FDCs) are believed to be registered with the DRAP, and the limited data on their utilization makes it very difficult to understand the situation, thus almost impossible to design the locally relevant interventions to promote

rational use of medicines. Thus, an indirect way to generate and describe drug utilization statistics and their consumption patterns is by using computer databases.

## 2.4 Classification of Medicines:

Under the anatomical therapeutic chemical (ATC) classification system, medicines are classified on five levels starting with fourteen main organ or system groups followed by their therapeutic, pharmacological, and chemical properties [8]. Anti-infective for systemic use are classified under the organ class J while antibacterial for systemic use are J01. In the same organ class based on the pharmacological and chemical properties, cephalosporins are J01D, and fluoroquinolones are J01MA, as explained in Figure 3.[9].

Figure 3: Classification of Cephalosporins and Fluoroquinolones under ATC.



Antibiotics are also classified by WHO in to three groups named 'Access', 'Watch' and 'Reserve' to combat antimicrobial resistance as each group specifies which antibiotics to be used as empiric (first or second line), cautiously or as a last recourse [10, 11].

## **2.5 Units of Measurement:**

The main unit of measurement is defined daily dose (DDD), which is an average daily maintenance dose of a medicine for adults in its main indication. DDD standardizes a large sales statistic usually presented as units, tablets, capsules, or different other dosage forms to present an estimate about the number of people exposed to a certain medicine [12]. In the case of antimicrobials that are used for a shorter duration, the unit is expressed as DDDs per 1000 inhabitant per day (DID), which estimates the number of persons per 1000 treated with one DDD with a particular medication every day.

In the present study, to estimate the presence of registered antimicrobials, five year consumption trend for cephalosporins and fluoroquinolones, and the fixed dose combinations in Pakistan, a regularly maintained drug sales dataset from IQVIA Pakistan was used.

## **2.6 IQVIA**

IQVIA, formerly Quintiles and IMS Health, Inc, is an international data science company founded in 1982 as Quintiles Transnational. IQVIA Pakistan (formerly IMS, Pakistan) has been operating in Pakistan since 1967 and is regarded as a good enough reliable source with updated sales data on the registered medicines in the country. It offers multiple data products to the pharmaceutical industry in Pakistan, but the one which gives a more general overview of the total Pakistan retail market is Pakistan Pharmaceutical Index (PKPI). The software version of which is called IMSPlus [13].

IQVIA data is a retail audit capturing sales directly from more than 1000 distributors[13] to pharmacies, whole-sellers, and retail pharmacies in small private hospitals. In the case of Pakistan, this database comprises of 85% actual sales, and 15% projected data for companies not sharing their distributor's data. In each sector, data is collected monthly to record direct sales from the manufacturer's designated distributors. This data is granulated into regional, city, and brick-level for different distribution-channels [14].

The initial list categorizes the sales data according to brand names, molecular compositions along with their annual sales figures, but for study purposes, the analysis was kept for molecular compositions only. Brief methodologies used for the three studies explained in chapters 3, 4, and 5 are as follows.

## **2.7 Study 1: Antimicrobials in Pakistan**

To study antimicrobial drugs in Pakistan, we extracted March 2019 IQVIA Pakistan data, which included sales units from the last 12 months for the J01 ATC subgroup (antimicrobials for systemic use). The file included all AM containing registered brands and presentations currently being sold in the country. WHO's Essential Medicines List 2019 [15] and National Essential Medicines List of Pakistan from 2018 [16] was used as a reference for the analysis.

For the classification of the different antimicrobials, the Anatomic Chemical Therapeutic (ATC) classification proposed by the WHO Collaborating Center for Drug Statistics Methodology in Oslo (Norway) was used for the systemic use group (J01) and its ten subgroups. Additionally, each AM was classified according to the WHO *AWaRe* classification, as "Access," "Watch," and "Reserve" antimicrobials [17].

## **2.8 Study 2: Cephalosporins & Fluoroquinolones Consumption**

To estimate the national antibiotic consumption for the cephalosporins (Anatomic Therapeutic Chemical [ATC] classification J01D group) and fluoroquinolones (ATC J01MA group) using the IQVIA Pakistan data for five years from April 2014 to March 2019 was used. IQVIA data was presented in units that represent a unit carton of a certain number or volume of tablets, capsules, or liquids. These were converted into defined daily doses (DDD) using the ATC Classification System (ATC/DDD, 2019) developed by the WHO Collaborating Centre for Drug Statistics Methodology [9]. The number of DID (DDD per 1,000 inhabitants per day) was calculated using population estimates from the 2017 national census.

The WHO *AWaRe* classification was used, including 'Access', 'Watch', and 'Reserve' antimicrobials [17] and as a reference, 2019 WHO Essential Medicines List (WEML) was used [15].

## **2.9 Study 3: Fixed dose Combinations in Pakistan**

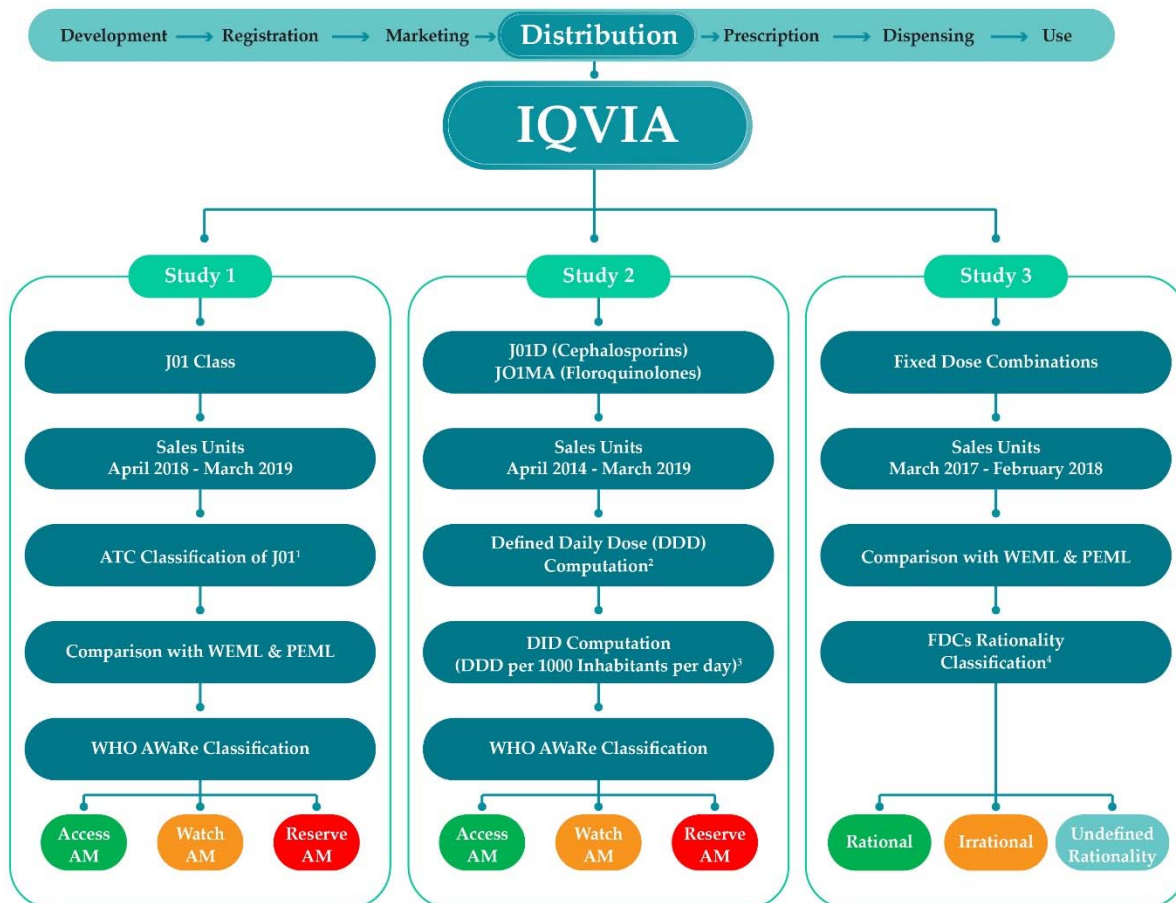
To identify FDCs currently being sold in the country, we extracted February 2018 IQVIA Pakistan data, which included sales units from the last 12 months. This was an indirect indicator of the FDCs marketed in the country. To analyze the rationality of each FDC, first, the National Essential Medical List of Pakistan 2018 (PEML) was compared with the WHO's model list of essential medicines, 2017 (WEML), to develop an understanding of the similarities and differences for FDCs in both lists [16, 18].

After excluding products containing multivitamins, a stepwise approach was taken to analyze the rationality of the FDCs containing pharmaceutical ingredients, which were

classified according to the Anatomical Therapeutic Chemical classification (ATC) principles [19].

FDA's *Orange Book*, [20], Stockley's Drug Interaction book; [21], published literature and other international lists of irrational or withdrawn drugs were used to determine their appropriateness or withdrawal status market [22-25]. These combinations were then compared with the list of FDCs currently being sold in Pakistan to estimate the presence of irrational combinations in the Pakistani market. Figure 4 presents the methodologies of three studies.

Figure 4: Figure Explaining the Methodology of the Conducted Studies.



- 1 For the classification, the ATC classification proposed by the WHO Collaborating Center for Drug Statistics Methodology in Oslo (Norway) was used for the systemic use group (J01) and its ten subgroups.
- 2 Calculated using the ATC Classification System (ATC/DDD, 2019) developed by the WHO Collaborating Centre for Drug Statistics Methodology
- 3 Calculated using population statistics from Census 2017
- 4 Classified based on 1) Active ingredients 2)FDC's Orange book 3)Stockley's Drug Interactions 4)Internationally withdrawn Drug list. (Detail in Figure 7)

## 2.10 References

1. Committee, W.E., *The Selection of Essential Drugs*. 1977, World Health Organization Geneva.
2. Figueras, A. and J.R. Laporte, *Failures of the therapeutic chain as a cause of drug ineffectiveness*. *BMJ*, 2003. **326**(7395): p. 895-6.
3. World Health Organization, *MDS-3: Managing Access to Medicines and Health Technologies*. 2012, Arlington, VA: Management Sciences for Health.
4. Bachhav, S.S. and N.A. Kshirsagar, *Systematic review of drug utilization studies & the use of the drug classification system in the WHO-SEARO Region*. *Indian J Med Res*, 2015. **142**(2): p. 120-9.
5. David, L. and U. Bergman., *Studies of Drug Utilization*, in *Pharmacoepidemiology*. 2012. p. 377-401.
6. World Health Organization, *Introduction to drug utilization research*. 2003: World Health Organization.
7. Stolar, M.H., *Drug use review: operational definitions*. *American Journal of Health-System Pharmacy*, 1978. **35**(1): p. 76-78.
8. World Health Organisation. *Anatomical Therapeutic Chemical (ATC) Classification*. Available from: [https://www.who.int/medicines/regulation/medicines-safety/toolkit\\_atc/en/](https://www.who.int/medicines/regulation/medicines-safety/toolkit_atc/en/) (accessed on 25 September 2019).
9. World Health Organisation, *WHO Collaborating Centre for Drug Statistics Methodology* 2018.
10. World Health Organisation., *The selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th Model List of Essential Medicines for Children)*. 2017: World Health Organization.
11. World Health Organisation. *In the face of slow progress, WHO offers a new tool and sets a target to accelerate action against antimicrobial resistance*. Adopt AWaRe: Handle Antibiotics with care 2019; Available from: <https://www.who.int/news-room/detail/18-06-2019-in-the-face-of-slow-progress-who-offers-a-new-tool-and-sets-a-target-to-accelerate-action-against-antimicrobial-resistance> (accessed on 25 September 2019).



12. World Health Organization, *Guidelines for ATC classification, and DDD assignment 2013*. Norwegian Institute of Public Health. Oslo, 2009.
13. Pakistan, I. *About IQVIA Pakistan*. 2018; Available from: <https://www.iqvia.com/locations/pakistan/about-iqvia-pakistan> (accessed on 24 September 2019).
14. IQVIA/IMS. *Gain the most accurate and reliable view of market demand*. Available from: <https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information> (accessed on 24 September 2019).
15. World Health Organization. *WHO Model List of Essential Medicines 21st list*. 2019; Available from: <https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1> (accessed on 08 September 2019).
16. Drug Regulatory Authority, P. *National Essential Medicines List NEML 2018*. 2018; Available from: <http://www.dra.gov.pk/Home/PharmacyServices> (accessed on 24 September 2019).
17. Hsia, Y., et al., *Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries*. *Lancet Glob Health*, 2019. 7(7): p. e861-e871.
18. World Health Organisation. WHO. *WHO Model Lists of Essential Medicines. Essential medicines and health products 2017*; Available from: <https://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1> (accessed on 4 July 2019)
19. WHO. Collaborating Centre for Drug Statistics Methodology, *Guidelines for ATC classification and DDD assignment 2019*. 2018.
20. US Food and Drug Administration, F., *Orange Book Data Files. Electronic Resource*. 2018.
21. Van Mil, J.W.F., *Stockley's drug interactions 11th edition*. Vol. 38. 2016.
22. Gautam, C.S. and S. Aditya, *Editorial - Irrational drug combinations: Need to sensitize undergraduates*. *Indian Journal of Pharmacology*, 2006. 38(3): p. 169-70.
23. Siramshetty, V.B., et al., *WITHDRAWN—a resource for withdrawn and discontinued drugs*. *Nucleic Acids Research*, 2015. 44(D1): p. D1080–D1086.
24. National Health Portal, N. *Complete list of 344 drugs banned by the Ministry of Health Family welfare*. 2016; Available from:

[http://www.cdsc0.nic.in/writereaddata/fdcreport10\\_2\\_2016.pdf](http://www.cdsc0.nic.in/writereaddata/fdcreport10_2_2016.pdf) (accessed on 24 September 2019).

25. Raju, K., A. Elumalai, and E. Sridhar, *Irrational Drug Combinations*. International Journal of Experimental Pharmacology, 2013. **3**(2): p. 52-56.

## **Chapter 3 :**

### **Analysis of the Antimicrobial Market in Pakistan: Is It Really Necessary Such a Vast Offering of “Watch” Antimicrobials?**

**Farrukh Malik**

**Albert Figueras**

**Antibiotics** 2019, 8(4), 189; <https://doi.org/10.3390/antibiotics8040189>

Published: 17 October 2019

### 3.1 Abstract

**Introduction:** Understanding antimicrobials (AM) on offer in a pharmaceutical market with a particular reference to drugs categorized as “Watch” active ingredients is one of the important steps to assess their potentially inappropriate use.

**Methods:** The March 2019 data with all AM containing registered brands and presentations currently being sold in the country for the J01 ATC subgroup from IQVIA Pakistan was used. Each AM was categorized as “Access,” “Watch,” or “Reserve,” according to the WHO AWaRe classification.

**Results:** There were 59 single chemical entities and 14 combinations with 1869 brands and 4648 presentations. The WHO Essential Medicines List included 35 J01 AM while an additional 38 single and combination AM with 425 brands & 977 presentations were present in the country. Looking at the whole list of marketed AM, 8 of the 10 AM with more than 60 brands were classified as “Watch”, offering 962 brands and 2418 presentations.

**Conclusion:** Most AM marketed in Pakistan with an excessive number of brands belong to the “Watch” AWaRe category. Higher the number of brands, higher will be the marketing pressure on prescribers and pharmacists and more potential confusion. One vital step to rationalize the use of AM lies in reviewing their market offer.

## 3.2 Introduction

In 1980, PKM Lunde wrote that “there has been no proof of greater public health benefits with an infinite number of drugs” [1] and, to our knowledge, four decades later, nobody has proven the contrary. Additionally, in the case of antimicrobials (AM), an excess could be linked with higher resistance rates. Medicines marketed in a country are the result of cumulative marketing authorizations under different legal frameworks along with the history, some of them even before the modern evidence-based decisions Era. So, as recommended by WHO, the first step to rationalize the use of medicines consists of an analysis of the pharmaceutical market [2].

Global AM market generated revenues of 42,335 million US\$ in 2017, with projections of more than \$50,000 million by 2025. Much of this growth is attributed to increased consumption of antibiotics in low & middle-income countries. Beta-lactam antibacterials and formulations, including beta-lactamase inhibitors, are and will be the most commonly prescribed antibiotics, followed by quinolones [3].

Over the next five years, Pakistan is expected to be among the top three developing countries with the fastest growth for medicines spending [4], which indicates a high consumption trend for antibiotics, with physicians having insufficient knowledge about their appropriate prescription [5], making it the third-highest consumer of antibiotics among lower and middle-income countries (LMIC) [6]. The risk of developing resistance significantly increases with the inappropriate use of antibiotics. Indeed, the growing AMR phenomenon has been dubbed as the ‘biggest threats to modern medicine’ [7].

Antibiotics are categorized by WHO into three groups named ‘Access’, ‘Watch’ and ‘Reserve’, a classification aimed at advising on how the different antibiotics should be available, selected, and prescribed. Thus, the so-called ‘AWaRe’ classification is also presented as a tool to help in the Global combat to antimicrobial resistance as each group

specifies which antibiotics to be used as empiric (first or second line), cautiously or as a last recourse [8, 9]. The global rise in antibiotic resistance demonstrates that ill-coordinated efforts cannot help curb the challenge. When determining factors, apart from the biological predisposition of the organism to outgrow its threat, humanistic factors must be evaluated. The role of human decisions in terms of prescription, dispensing, prevention, self-use, and use in other sectors such as animals, are all important factors to study. Other macro-contributors to the phenomenon include the community, the environment, healthcare settings, and fragments and cracks in regulatory processes and systems to prevent antibiotic abuse [10]. The global antimicrobial stewardship program may serve as a platform to bring together these disparaging concerns and findings to make *sense* of the madness of overprescribing. As evident from sales data of Pakistan, the need to create multiple *me-too* of the same generic, and even more so, its sales in such high numbers is precisely the reason why international and local collaborations must take place under strict regulatory frameworks.

The healthcare system in Pakistan is one of the most challenged systems due to the least amount of GDP it receives to sustain itself, with less than 3% of GDP spent in 2016 [11]. The system is based on out of pocket payment, where services are given progressively according to the severity of the medical condition in primary, secondary, and tertiary care facilities [12]. The poor standards of care, and lack of resources, along with pressure from patients for medications from their care provider, all contribute towards antibiotic prescriptions.

Furthermore, there is a need to create and adhere to robust prescribing guidelines, which can help mitigate the irrational use of antibiotics [5].

The indicators developed by WHO have helped identify systematically the complex interplay of these factors and how, by keeping a close watch, improvements were achieved in reducing the usage of medicines in various regions. By setting surveillance methods, improvements were made in reducing the usage of medicines in various regions [13].

The National Strategic Framework for the Containment of Antimicrobial Resistance was adopted in 2017 as a national action plan to address the growing concern of antibiotic use and resistance. From the carried out work, multiple factors were identified as contributory to the challenge. Firstly, the number of antibiotics available in the Pakistani market is very high. Further, highly prevalent self-medication behavior and up to 70% of patients prescribed with antibiotics [14].

Antimicrobial stewardship should begin with a rational market offer of the available brands to be prescribed. Thus, the aim of the present study was to describe the antibiotics medicine offerings in Pakistan, with a particular reference to drugs that have been categorized as “Watch” active ingredients.

### **3.3 Materials and Methods**

The March 2019 data, which included sales units from the last 12 months for the J01 ATC subgroup (antimicrobials for systemic use) from IQVIA Pakistan, was used. Like many other LMICs, Pakistan lacks an updated official database for the authorized products with their sales and prescription figures. IQVIA Pakistan produces multiple types of retail data sets, but for the present research, Pakistan Pharmaceutical Index (PKPI) was accessible to study the pharmaceutical market as an indirect measure.

The file included all AM containing registered brands and presentations currently being sold in the country.

As a reference for the analysis, the 2019 edition of the World Health Organization Essential medicines List (WEML) [15] and the 2018 edition of the National Essential Medicines List of Pakistan (PEML) were used.

For the classification of the different antimicrobials, the well-recognized Anatomic Chemical Therapeutic (ATC) classification proposed by the WHO Collaborating Center for Drug Statistics Methodology in Oslo (Norway) was used, specifically, the antibacterials for systemic use group (J01) and its ten subgroups [16].

Additionally, each AM was classified according to the WHO AWaRe classification, as “Access,” “Watch,” and “Reserve” antimicrobials. ‘Access’ antibiotic should be the first choice for the most common infections, while ‘Watch’ includes most of the “highest-priority critically important antimicrobials recommended only for specific, limited indications. ‘Reserve’ antibiotics should only be used as a last resort when all other antibiotics have failed”[17].

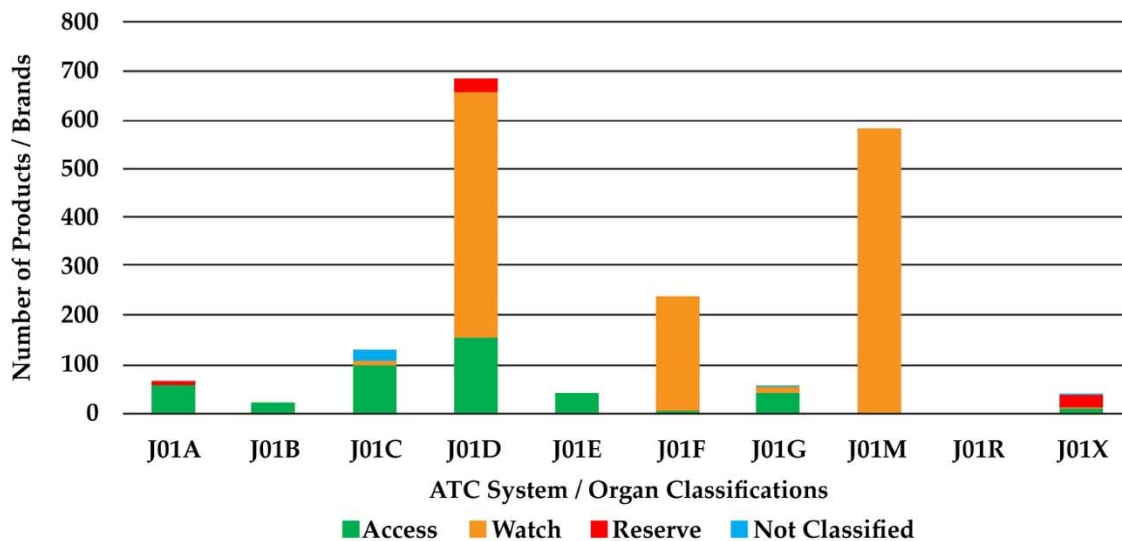
### **3.4 Results**

Fifty-nine single chemical entities and 14 combinations belonged to the J01 ATC subgroup in Pakistan; there were 1869 brands containing one of these AM (median = 65 brands/AM; range = 23 - 684) and 4648 presentations (median = 130; range = 37 – 1981). The WEML included 35 AM under the ATC group J01. In Pakistan, an additional 38 single and combination AM were present with 425 brands and 977 presentations.

A high number of brands for antimicrobials belonged to the ATC subgroups J01M (Fluoroquinolones) and J01F (Macrolides), both of which are classified as the “Watch” category. Also, part of antimicrobials under ATC J01D (Cephalosporins) are classified as “Watch” (Figure 5).



Figure 5: Distribution of the number of brands of all Antimicrobials for systemic use present in the country according to the ATC classification, according to the WHO AWaRe classification.



J01A = tetracyclines; J01B = amphenicols; J01C = beta-lactam antimicrobials, penicillins; J01D = other beta-lactam antimicrobials; J01E = sulphonamides and trimethoprim; J01F = macrolides, lincosamides and streptogramins; J01G = aminoglycoside antibacterials; J01M = quinolone antibacterials; J01R = combinations of antibacterials; J01X = other antibacterials.

The National Essential Medicines List of Pakistan (PEML) contains 31 AM from J01 class, while 6 AM (including one combination) present in the WEML were absent from the PEML, which belonged to the “Watch” or “Reserve” groups. These AMs included Cefuroxime, Cefuroxime Axetil, Cefotaxime, Imipenem+Cilastatin, Trimethoprim, & Fosfomycin with at least 103 brands (median 9.5, range = 2-62) and 238 presentations.

An in-depth analysis of the 38 additional AM, which were not considered in the WEML but available in the Pakistan market, showed that the number of brands per AM had a median value of 4.5 (range = 1-90). The top 20 AMs of these included 13 AM are classified as “Watch” and two classified as “Reserve” with 229 brands with a median value of 14 (range = 4-31) & 408 presentations Table 1).

Table 1: Top 20 antimicrobials not considered in the WHO-EML but available in the Pakistan market according to the number of brands and presentations per active ingredient and classified according to the WHO *AWaRe* categories.

S.No.	AWaRe Category	ATC	Active ingredient	Brands (n)	Presentations (n)
1.	Access	J01DB09	Cefradine	90	345
2.	Access	J01DB05	Cefradoxil	43	111
3.	Watch	J01DD62	Cefoperazone + Sulbactam	31	62
4.	Watch	J01FF02	Lincomycin	31	51
5.	Watch	J01MA15	Gemifloxacin	24	24
6.	Reserve	J01DE01	Cefepime	24	44
7.	Watch	J01FA06	Roxithromycin	21	36
8.	Watch	J01DC04	Cefaclor	19	76
9.	Watch	J01DD13	Cefpodoxime Proxetil	16	36
10.	Access	J01AA06	Oxytetracycline	14	17
11.	Watch	J01MA06	Norfloxacin	14	15
12.	Watch	J01MA09	Sparfloxacin	12	13
13.	Not classified	J01CR50	Ampicillin + Cloxacillin	11	31
14.	Watch	J01GB04	Kanamycin	9	15
15.	Watch	J01MA03	Pefloxacin	7	7
16.	Watch	J01DD12	Cefoperazone	6	10
17.	Watch	J01GB01	Tobramycin	6	9
18.	Reserve	J01AA12	Tigecycline	5	5
19.	Not classified	J01CR50	Axoxicillin + Flocoxacin	5	11
20.	Watch	J01MA16	Gatifloxacin	4	5

Looking at the whole list of marketed AM in Pakistan, 8 of the 10 AM with more than 60 brands in the market were classified as “Watch”, with 442 brands and 973 presentations of the different fluoroquinolones (ATC group J01M), 350 brands and 1060 presentations of third-generation cephalosporins (ATC subgroup J01DD) and 170 brands and 385 presentations of macrolides (ATC subgroup J01F).

It should be noted that for five “Reserve” group AM, which included two 4th generation cephalosporins (ATC subgroup J01DE), there were 57 brands available in the country.

### **3.5 Discussion**

The main result of the present analysis of the antimicrobials available in the Pakistan market is the apparently excessive number of brands per active ingredient, which can be worrying in the particular case of some “Watch” and “Reserve” antimicrobials not included in the WHO Essential Medicines List. This is the case of lincomycin or the combination cefoperazone + sulbactam (with 31 different brand-names each), or the “Reserve” 4<sup>th</sup> generation cephalosporin cefepime, with 24 different brand names.

On the one hand, more available brand names of a single active ingredient mean more market pressure and, hence, more chances to be prescribed irrationally [18]. On the other hand, the high presence of “Watch” antibiotics in a market already saturated with countless combinations (rational and irrational) bears serious thought for policymakers and regulators [13].

Pakistan has become a fertile ground for promoting antibiotics, as the market regulations for medicines are weak, and the growth potential for generics (branded) is very high. There is a growing need to identify potential for harm or other interventions that can take place due to the high use of medicines in countries with lower socioeconomic countries [19].

Interestingly, despite reports of antibiotics being regularly out of stock in many of the Pakistani public healthcare facilities, their sales are high in different pharmacies and regions. These primary healthcare facilities lack proper standard treatment guidelines for prescribers, with the result that almost 80% of the prescriptions in both outpatient and inpatient departments were found improper, and the most commonly prescribed antibiotics included fluoroquinolones, cephalosporins, and penicillins [20].

Due to misinformation amongst doctors as well as the general public, there is widespread use and buying behavior towards broad-spectrum antibiotics, that are not followed through, leaving the antibiotic course in the middle [21], which poses a challenge in collating results, which may require more robust surveillance controls. Many solutions are being proposed to address concerns on medication safety, particularly the growing use of antibiotics. Alongside the need for systems that ensure the safety of medication use, there is a concurrent need for ensuring that guidelines developed must be aligned to international treatment standards.

The role of microbiologists should also be promoted as a way to improve the selection of the most appropriate antimicrobials for the patients in need of them, and this is especially relevant for “Reserve” AM [22].

In a recent effort to the antibiotic use, the pharmacies in the capital Islamabad have been directed to keep a check on the number of antibiotics sold and that they shouldn't be dispensed without prescription [23]. Despite this, dispensing without prescription is high in the country, and an excessive number of brands help to increase the irrationality of the decisions also at the pharmacy level.

The present research is a cross sectional study of the pharmaceutical market of antimicrobials in Pakistan based on data for the authorised medicinal products in the country. The main limitation is that the data source did not give any information on the

products which were approved but had no recorded sales. Anyway, the study identified all antimicrobials available for prescription in the country; thus, it provided information on the wide range of different brands and presentations for a single active ingredient and combinations, and this was the main purpose of the analysis.

Although the findings of this study are not unique to Pakistan and there have been similar findings in other LMICs where only 50% of all the newly registered products were from the WHO's essential medicines list [24]. Medicines market analyses such as the present one are quite simple to conduct and provide a general panorama of the products available in pharmacies of a given country. A careful observation of the results could show either irrational products marketed before the 'Evidence-based medicine Era' or, as in the present case, an apparently unnecessary plethora of products with the same composition but different brand names which go beyond what could be considered a balanced assorted market. Countries could conduct these analyses as the first step in their antimicrobial stewardship programs.

### **3.6 Conclusion**

In summary, Pakistan is a country facing high rates of antibiotic resistance; the excessive and apparently unnecessary high number of registered antibiotics available in the market, coupled with excessive use and prescription rates of these drugs, and lack of regulatory controls to counter irrational antibiotic prescription patterns could help to explain the present situation.

Most of the AM marketed in Pakistan belong to the "Watch" AWaRe category. With the marketing competitiveness of various brands at play and a higher number of brands available of a generic drug, more marketing pressure is likely to be applied to prescribers and pharmacists or vice versa. The inconsistent prescribing information for the same product in different countries has been observed, which could have a detrimental impact

on a patient [25]. This may also increase the potential for confusion when prescribing antibiotics medications are readily available over the counter without the need for prescriptions, further worsening the situation. As evidenced by sales data, the Pakistani market is currently selling the same generic under multiple brand names. In this regard, packaging and critical information displayed on the packaging are important contributors to the quality of the information provided. It was found in a survey in the USA that over 33% of medication errors took place due to packaging issues or confusing information on the packaging [26].

This is just one example of how multiple branded generics under different names can cause confusion. In a market like Pakistan, where there is a lack of quality national resources for physicians to refer to for prescribing practices, the presence of multiple branded generics can lead to errors. Other contributors, including marketing distractions, similar brand names for different products, misleading information on packaging, hidden drug fact labels, differing strengths and consumption methods, absence of visible warnings, and hidden ingredients may pose health risks [26]. In the case of antibiotics, physicians may be prone to make errors when prescribing doses, a matter that bears further investigation.

So, there is a need to rationalize the use of AM by rigorously reviewing the AM market offer in light of international guidelines and standards. Further, physicians must be educated and informed about the dangers of antibiotic resistance, encouraged to use antibiotics with caution, and made aware of their role in the prevention of this dangerous development.

### 3.7 References

1. Lunde, P.K.M., 'Drug and product selection-an essential part of the therapeutic benefit risk ratio strategy? Drug-induced Sufferings, Excerpta Medica, Amsterdam, 1980: p. 129-36.
2. World Health Organisation. *The Selection of Essential Medicines WHO Policy Perspectives on Medicines*, No. 4 2002; Available from: <https://apps.who.int/medicinedocs/en/d/Js2296e/> (accessed on 05 October 2019).
3. Sumant, O., T. Kunsel, and S. Pandey. *Global Antibiotics Market: Opportunities and Forecasts 2018-2025*. Allied Market Research. 2018; Available from: <https://www.alliedmarketresearch.com/antibiotics-market> (accessed on 08 September 2019).
4. IQVIA. *The Global Use of Medicine in 2019 and Outlook to 2023. Forecasts and Areas to Watch*. 2019; Available from: <https://www.iqvia.com/institute/reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023> (accessed on 08 September 2019).
5. Saleem, Z., et al., *Antimicrobial prescribing and determinants of antimicrobial resistance: a qualitative study among physicians in Pakistan*. Int J Clin Pharm, 2019.
6. Klein, E.Y., et al., *Global increase and geographic convergence in antibiotic consumption between 2000 and 2015*. Proc Natl Acad Sci U S A, 2018. **115**(15): p. E3463-E3470.
7. OECD. *Stemming the Superbug Tide*. 2018; Available from: <https://www.oecd-ilibrary.org/content/publication/9789264307599-en> (accessed on 08 September 2019).
8. World Health Organisation., *The selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th Model List of Essential Medicines for Children)*. 2017: World Health Organization.
9. World Health Organisation. *In the face of slow progress, WHO offers a new tool and sets a target to accelerate action against antimicrobial resistance*. Adopt AWaRe: Handle Antibiotics with care 2019; Available from: <https://www.who.int/news-room/detail/18-06-2019-in-the-face-of-slow-progress-who-offers-a-new-tool-and-sets-a-target-to-accelerate-action-against-antimicrobial-resistance> (accessed on 25 September 2019).



10. Roca, I., et al., *The global threat of antimicrobial resistance: science for intervention*. *New microbes and new infections*, 2015. **6**: p. 22-29.
11. PPI. *Health spending less than one percent of GDP for decades*. 2019; Available from: <https://www.pakistantoday.com.pk/2019/07/01/health-spending-less-than-one-percent-of-gdp-for-decades/> (accessed on 27 September 2019).
12. Hassan, A., K. Mahmood, and H.A. Bukhsh, *Healthcare System Of Pakistan*. *International Journal of Advanced Research and Publications*, 2017. **1**(4).
13. World Health Organization. *WHO Surveillance of Antimicrobial Use*. 2019; Available from: [https://www.who.int/medicines/areas/rational\\_use/AMU\\_Surveillance/en/](https://www.who.int/medicines/areas/rational_use/AMU_Surveillance/en/) (accessed on 08 September 2019).
14. Ministry of National Health Services Regulations and Coordination, M. *National AMR Action Plan for Pakistan*. 2017; Available from: <https://www.nih.org.pk/wp-content/uploads/2018/08/AMR-National-Action-Plan-Pakistan.pdf> (accessed on 08 September 2019).
15. World Health Organization. *WHO Model List of Essential Medicines 21st list*. 2019; Available from: <https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1> (accessed on 08 September 2019).
16. World Health Organisation, *ATC/DDD Classification*. *WHO Drug Information*, 2002. **16**(3).
17. Hsia, Y., et al., *Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries*. *Lancet Glob Health*, 2019. **7**(7): p. e861-e871.
18. Figueras, A. and J.R. Laporte, *Failures of the therapeutic chain as a cause of drug ineffectiveness*. *BMJ*, 2003. **326**(7395): p. 895-6.
19. Sheikh, A., et al., *Agreeing on global research priorities for medication safety: an international prioritisation exercise*. *J Glob Health*, 2019. **9**(1): p. 010422.
20. Sarwar, M.R., et al., *Antimicrobial use by WHO methodology at primary health care centers: a cross sectional study in Punjab, Pakistan*. *BMC Infect Dis*, 2018. **18**(1): p. 492.
21. Centre for Disease Dynamics Economics & Policy, C. *Situation analysis report on antimicrobial resistance in Pakistan*. 2018; Available from: <https://cddep.org/wp-content/uploads/2018/03/Situational-Analysis-Report-on-Antimicrobial-Resistance-in-Pakistan.pdf> (accessed on 08 September 2019).



22. Martins, T., et al., *Non-adherence to treatment recommendations is a factor contributing to the clinical failure of daptomycin: cohort study in Brazil*. Br J Pharm Sci 2019, 2019: in Press.
23. Ikram, J. *Sale of Antibiotic to be Regulated in Islamabad*. DAWN 2019; Available from: <https://www.dawn.com/news/1478847> (accessed on 08 September 2019).
24. Figueras, A., et al., *Health needs, drug registration and control in less developed countries--the Peruvian case*. Pharmacoepidemiol Drug Saf, 2002. **11**(1): p. 63-4.
25. Reggi, V., et al., *Prescribing information in 26 countries: a comparative study*. European journal of clinical pharmacology, 2003. **59**(4): p. 263-270.
26. Bootman, J., *Committee on Identifying and Preventing Medication Errors*, Aspden P, Wolcott JA, Bootman JL, Cronenwett LR ed. *Preventing Medication Errors: Quality Chasm Series*. Institute of Medicine. 2006, The National Academies Press, Washington, DC.

## **Chapter 4 :**

# **Continuous rise in cephalosporin and fluoroquinolone consumption in Pakistan: a 5 year analysis (2014 – 18)**

**Farrukh Malik**

**Albert Figueras**

*JAC-Antimicrobial Resistance*, Volume 1, Issue 3, December 2019, dlz063,  
<https://doi.org/10.1093/jacamr/dlz063>

Published: 13 November 2019

## 4.1 Abstract

**Introduction:** Pakistan was third on the list of the highest antibiotic consuming countries among low and middle-income countries in 2015. Studies have suggested that countries with higher consumption of antibiotics are likely to have higher antibiotic resistance rates.

**Objectives:** With limited surveillance data on consumption and resistance in Pakistan, this study investigated the five year trends (April 2014 to March 2019) in consumption of the two highest sold antibiotic classes, including cephalosporins (ATC group J01D) and fluoroquinolones (ATC group J01MA).

**Methods:** IQVIA Pakistan data (retail) on antibiotic sales presented in units were used. These data were standardised and assigned a defined daily dose to all formulations based on WHO's ATC/DDD index and the data expressed as DIDs (defined daily doses per 1,000 inhabitants per day). WHO's AWaRe classification of antimicrobials were used for the analyses, especially of those categorised as 'Watch'.

**Results:** The findings showed a significant increase in consumption trends for 'Watch' cephalosporins (61.5%) while the use of 'Reserve' cephalosporins doubled during the studied period. Combined consumption of 2nd and 3rd generation cephalosporins (both 'Watch' group) was nearly five times higher in 2018 in comparison to the 1st generation cephalosporins. For fluoroquinolones, the total consumption only majorly increased for ciprofloxacin with 127,820 more persons per day. The consumption of cephalosporins and fluoroquinolones in Pakistan increased by 1.86 DID in just five years.

**Conclusion:** It is urgent to establish a National Antimicrobial Commission in the country, to critically analyse the pharmaceutical market offer and implement surveillance systems and antimicrobial stewardship.

## 4.2 Introduction

Evidence has shown an association at an individual patient level between the prescribing of antibiotics in primary health care and antimicrobial resistance (AMR) in bacteria at different sites, with the strongest effects in the month after, but detectable for up to 12 months [1]. Since 2007 the antibiotic resistant bacteria related infections in Europe have continuously increased in comparison with other infections [2], and countries with higher consumption of antibiotics have higher AMR rates.[3]. Pakistan is the third highest antibiotic consuming country among low and middle-income countries (LMICs), and in sixteen years, the DDDs increased by 65%, and the consumption rates were 19.6 DDD per 1,000 inhabitants per day in 2015 [4].

While surveillance data has helped multiple countries realize and intervene on their high consumption of antibiotic use [5] absence of national surveillance data on consumption and resistance along with limited laboratory facilities is a significant hindrance to know the correct numbers and design the best interventions [6].

The emergence of *E. coli* strains resistant to 3<sup>rd</sup> generation cephalosporins, and fluoroquinolones are worrying [7] Similarly, there is resistance developing for extended-spectrum cephalosporins including 3<sup>rd</sup> and 4<sup>th</sup> generation in the Asian Pacific region since 2009 [8] and increasing and worrying exposure of these high-end cephalosporins has been observed in the pediatric population in Pakistan [9]. Multiple studies from Pakistan have shown *E. coli*, and *Klebsiella pneumoniae* to be significantly associated with Extended-spectrum-lactamases (ESBLs) production with one multicenter study showing ESBLs were suspected of producing 46% *E. coli* and 31.9% *Klebsiella* multidrug resistant pneumonia strain [10, 11]

Any sub-optimal level administration of antibiotics to the susceptible microorganism provides an opportunity to develop survival mechanisms hence contributing to antibiotic resistance.

The present study was planned to investigate the trends in the consumption of cephalosporins and fluoroquinolones antibiotics in Pakistan during five years.

### **4.3 Methods**

We estimated the national antibiotic consumption for the cephalosporins (Anatomic Therapeutic Chemical [ATC] classification J01D group) and fluoroquinolones (ATC J01MA group) using the IQVIA Pakistan data for five years (April 2014 to March 2019).

IQVIA data is a retail audit capturing sales directly from distributors to pharmacies, whole sellers, and retail pharmacies in small private hospitals. In the case of Pakistan, this database comprises of 85% actual sales, and 15% projected data for companies not sharing their distributor's data. In each sector, data is collected monthly to record direct sales from the manufacturer's designated distributors. This data is granulated into national, regional, city,brick (a group of pharmacies)-and pharmacy/medical stores level for different distribution-channels. IQVIA data on antibiotic sales are presented as brands and presentations, which are further shown as units that represent a unit carton of a certain number or volume of tablets, capsules, or liquids. All medicines in the country are available as innovator or generic brands and not as generics while each brand could have multiple dosage strengths (e.g., 5mg, 10mg or 20mg in the case of Rosuvastatin) called presentations All units were converted into defined daily doses (DDD) using the ATC Classification System and DDD methodology (ATC/DDD, 2019) developed by the WHO Collaborating Centre for Drug Statistics Methodology [12].

The number of DID (DDD per 1,000 inhabitants per day) was calculated using population estimates from the 2017 national census (207,770,000 inhabitants), as all other population numbers between 2013 and 2018 were estimates calculated with growth rate factored in. We used the biggest denominator in order to avoid overestimations in the first years.

In order to classify the different antimicrobials, the WHO *AWaRe* classification was used, including 'Access', 'Watch', and 'Reserve' antimicrobials [13]. As a reference, the 2019 WHO Essential Medicines List (EML) was used [14].

## 4.4 Results

Cephalosporins and fluoroquinolones were the highest selling anti-infective medicines in the country. The number of brands and presentations were 667 and 1,934, respectively, for cephalosporins, and 582 and 1,139 for fluoroquinolones.

### 4.4.1 Cephalosporin consumption

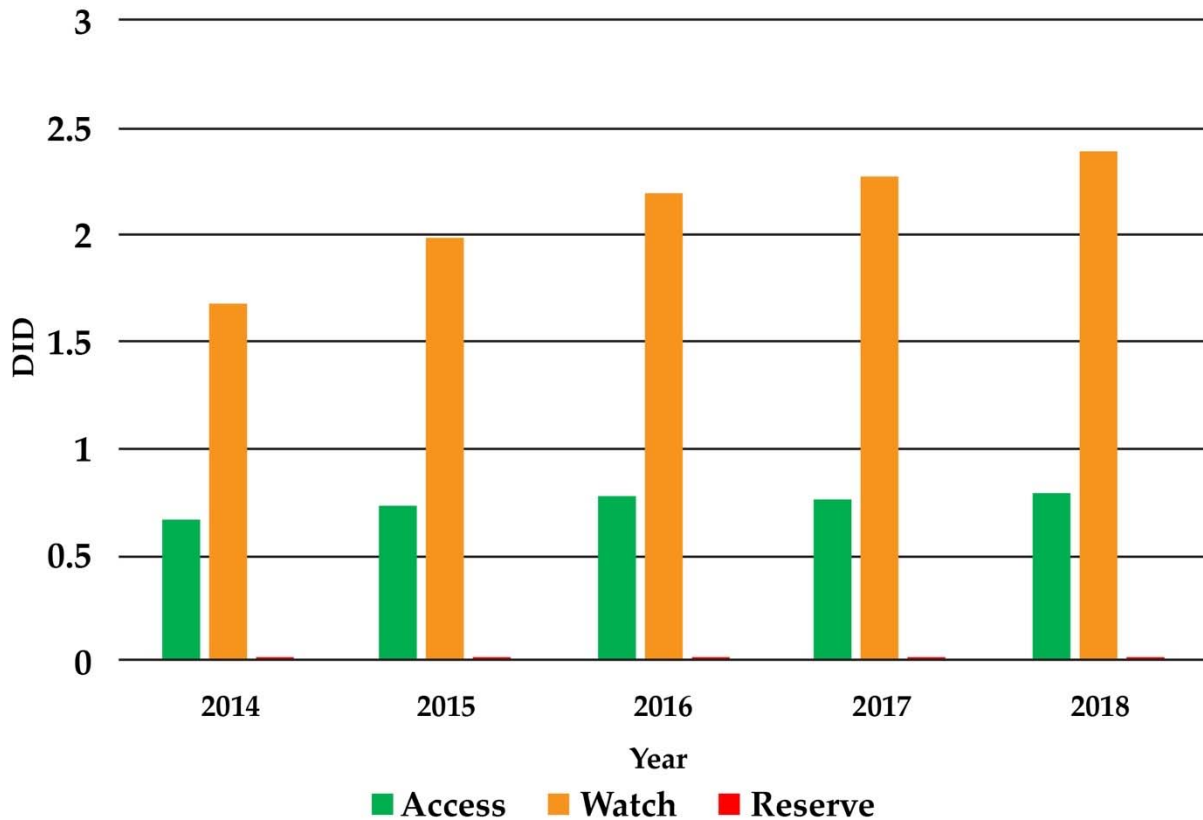
Over the five years studied, the net increase in the consumption for the whole class was 0.8609 DID (approximately 179,000 more people treated each day in 2018 as compared with 2014). The major increase was observed for molecules of the 3<sup>rd</sup> generation ('Watch' group) as their net increase was 0.8855 DID (approximately 184,000 more people treated each day at the end of the study).

The consumption of cephalosporins not included in the EML (0.6558 DID) was around 22% of the total consumed in 2018. Combined consumption of 2<sup>nd</sup> and 3<sup>rd</sup> generation – 'Watch' group – was nearly five times higher in 2018 in comparison to the sales of 1<sup>st</sup> generation – 'Access' group – (2.4463 and 0.5254 DID, respectively).

Thus, the population exposed to 'Watch' group cephalosporins increased from 315,000 inhabitants/day in 2014 to 508,000 inhabitants /day in 2018, while for 'Reserve' group –4<sup>th</sup>

generation– an estimated increased consumption from 311 inhabitants/day to 623 inhabitants/day meaning that the population treated daily with these highly important cephalosporins doubled in five years (see Figure 6).

Figure 6 : Five year DID sales trend for ‘Access’, ‘Watch’, & ‘Reserve’ Cephalosporins in Pakistan.



DID = Defined daily doses / 1,000 inhabitants / day.  
 Data Source: IQVIA Pakistan

The ‘Access’ cephalosporins deserve special comment. While there was a small increase in consumption for the ‘Access’ cephalosporins included in the EML, there was a decrease in the consumption of ‘Access’ cephalosporins not included in the EML. Notwithstanding this, it should be noted that the sales of cephalosporins not included in the EML were 4.5

times higher. In the case of 'Watch' cephalosporins, those included in the EML were 10 times more consumed than those not included in the EML (Table 2).

Table 2 : Evolution of the sales of Cephalosporins and Fluoroquinolones in Pakistan expressed in defined daily doses/1,000 inhabitants/day (DID) during the study period.

Antimicrobials		2014	2015	2016	2017	2018	Net Increase
<b>CEPHALOSPORINS</b>							
	<b>In EML</b>	0.0913	0.1008	0.0993	0.0988	0.0942	+0.0029
<b>Access</b>	<b>Not in EML</b>	0.5064	0.5827	0.4014	0.4134	0.4312	-0.0752
	<b>Total</b>	0.5977	0.6835	0.5007	0.5122	0.5254	-0.0723
	<b>In EML</b>	1.3678	1.6432	1.8610	2.0746	2.2247	+0.8569
<b>Watch</b>	<b>Not in EML</b>	0.1469	0.1868	0.2063	0.1963	0.2216	+0.0747
	<b>Total</b>	1.5147	1.830	2.0673	2.2709	2.4463	+0.9316
<b>Reserve</b>		0.0015	0.0018	0.0020	0.0025	0.0030	+0.0015
<b>Total Cephalosporins</b>		2.1139	2.5153	2.5700	2.7856	2.9747	+0.8608
<b>FLUOROQUINOLONES</b>							
<b>Ciprofloxacin</b>		1.5557	1.8000	1.9221	2.0543	2.1709	+0.6152
	<b>In EML</b>	1.9183	2.2220	2.3375	2.4148	2.3794	+0.4611
<b>Other</b>	<b>Not in EML</b>	0.2970	0.2909	0.2738	0.2567	0.2197	-0.0773
	<b>Total</b>	2.2153	2.5129	2.6113	2.6715	2.5991	+0.3838
<b>Total Fluoroquinolones</b>		3.7710	4.3128	4,5334	4.7258	4.7700	+0.9990

§ 'Access', 'Watch', and 'Reserve categories according to the AWaRe classification.

EML = 2019 WHO Essential Medicines List.

Data source: IQVIA-Pakistan



#### 4.4.2 Fluoroquinolone consumption

Regarding fluoroquinolone antimicrobials, all were considered under the 'Watch' group of the *AWaRe* classification. The net increase for the whole class during the study period was 0.9990 DID (approximately 208,000 more people were treated each day). The total consumption increase for ciprofloxacin was 0.6152 DID, while for all other quinolones was 0.3838 DID. It should be highlighted that the consumption of 'other quinolones' in 2018 (2.5991 DID) was higher than that of ciprofloxacin (2.1709 DID) (see Table 2).

### 4.5 Discussion

The present sales analysis of cephalosporin and fluoroquinolone antibiotics in Pakistan during five years showed a combined increase of 1.8598 DID, i.e., in 2018, an additional 386,000 patients were receiving one of these antimicrobials each day compared to 2014 when a total of 1223,000 patients were being treated each day. These figures are relevant because most of the consumed cephalosporins and all the fluoroquinolones belonged to the 'Watch' group; thus, special attention should be paid to their indications of use as well as actual treatment patterns.

There could be multiple factors driving the high consumption of cephalosporins and fluoroquinolones observed in Pakistan. Probably, an important driver of high and potentially inappropriate consumption is excessive prophylactic usage [15]. The data used for this study showed an enormously high number of presentations of these antimicrobials from multiple manufacturers generating significant annual revenues. Additionally, it should be taken into account that about 10-15% of antibiotics are believed to be spurious or falsified in the Pakistan market, with quinolones and cephalosporins as the most common classes, as both are perceived to be the best choice antibiotics by physicians and patients [6].

The underlying question is: “How many are too many when we are talking about antimicrobials?” Probably, the appropriate selection of antimicrobials by prescribers, according to clinical, microbiological, and pharmacological aspects, has an extraordinary role in improving the use of antimicrobials [16], but undoubtedly, the public policies are also effective to promote more rational use of medicines [17]. The absence of robust surveillance data limits the ability of the regulatory authorities to monitor the registrations, renewals, sales, and resistance patterns for high-risk antibiotics. In the case of Pakistan, the weaker healthcare regulations exacerbate the industry influence on the prescribers [6, 18] and it could be an important factor in what we see as an antibiotic flooded pharmaceutical market by a higher number of presentations than reasonably needed, as well as the coexistence of so many brand-names containing the same antimicrobial.

While physicians widely acknowledge the weak regulations in the country,[18] antibiotic stewardship programs (including education, formulary restriction, prior approval programs, streamlining, antibiotic cycling and automated or computer-assisted prescribing) [19] or increasing awareness and control of selling antimicrobials without prescription [20] are necessary for slowing the speed of antibiotic resistance.

The thread of antibiotic resistance in a developing country like Pakistan, where the population has limited access to education and healthcare services, is considerable. AMR will remain a major problem in managing various ever-evolving infections unless urgent steps are taken to control the influx of more brands and presentations of an already saturated market for cephalosporins and fluoroquinolones.

The present study has some limitations, being the most important that the data used are sales data, and do not necessarily mean actual consumption by patients. Despite this, IQVIA sales data are considered a proxy to consumption, and are exceptionally consistent

for time-comparisons within the same country, as is the case. Additionally, IQVIA sales data in Pakistan are not representative of hospital usage for inpatients and also does not explain the individual over the counter buying for self-medication. Despite this, due to the lack of any officially validated drug utilization data maintained at the provincial or federal government level, these results can be considered a first approach to the problem.

## **4.6 Conclusion**

The increasing use of 'Watch' cephalosporins and fluoroquinolones observed in Pakistan during the last five years raises huge concerns on its potential role in the growing AMR crisis. Critical analyses of the pharmaceutical market in Pakistan, as well as the promotion of surveillance systems based on drug utilization data at individual level, are urgent needs in order to try to increase the awareness of society in general and health professionals in particular and, at the same time, try to reduce the chances of unnoticed exposure to these antibiotics which should be reserved for the patients in need of them.

## 4.7 References

1. Costelloe, C., et al., *Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis*. *BMJ*, 2010. **340**: p. c2096.
2. Cassini, A., et al., *Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis*. *Lancet Infect Dis*, 2019. **19**(1): p. 56-66.
3. Goossens, H., et al., *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study*. *Lancet*, 2005. **365**(9459): p. 579-87.
4. Klein, E.Y., et al., *Global increase and geographic convergence in antibiotic consumption between 2000 and 2015*. *Proc Natl Acad Sci U S A*, 2018. **115**(15): p. E3463-E3470.
5. Goossens, H., et al., *National campaigns to improve antibiotic use*. *Eur J Clin Pharmacol*, 2006. **62**(5): p. 373-9.
6. Centre for Disease Dynamics Economics & Policy, C. *Situation analysis report on antimicrobial resistance in Pakistan*. 2018; Available from: <https://cddep.org/wp-content/uploads/2018/03/Situational-Analysis-Report-on-Antimicrobial-Resistance-in-Pakistan.pdf> (accessed on 08 September 2019).
7. Collignon, P., *Resistant Escherichia coli--we are what we eat*. *Clin Infect Dis*, 2009. **49**(2): p. 202-4.
8. Bertrand, X. and M.J. Dowzicky, *Antimicrobial susceptibility among gram-negative isolates collected from intensive care units in North America, Europe, the Asia-Pacific Rim, Latin America, the Middle East, and Africa between 2004 and 2009 as part of the Tigecycline Evaluation and Surveillance Trial*. *Clin Ther*, 2012. **34**(1): p. 124-37.
9. Ali, S.R., S. Ahmed, and H. Lohana, *Trends of empiric antibiotic usage in a secondary care hospital, Karachi, Pakistan*. *Int J Pediatr*, 2013. **2013**: p. 832857.
10. Abrar, S., et al., *Distribution of CTX-M group I and group III beta-lactamases produced by Escherichia coli and klebsiella pneumoniae in Lahore, Pakistan*. *Microb Pathog*, 2017. **103**: p. 8-12.
11. Fatima, S., et al., *Phenotypic expression and prevalence of multi drug resistant extended spectrum beta-lactamase producing Escherichia coli and Klebsiella pneumoniae in Karachi, Pakistan*. *Pak J Pharm Sci*, 2018. **31**(4): p. 1379-1384.

12. World Health Organisation. *WHO Collaborating Centre for Drug Statistics Methodology* 2018; Available from: [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/) (accessed on.
13. Hsia, Y., et al., *Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries*. *Lancet Glob Health*, 2019. **7**(7): p. e861-e871.
14. World Health Organization. *WHO Model List of Essential Medicines 21st list*. 2019; Available from: <https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1> (accessed on 08 September 2019).
15. Saleem, Z., et al., *A multicenter point prevalence survey of antibiotic use in Punjab, Pakistan: findings and implications*. *Expert Rev Anti Infect Ther*, 2019. **17**(4): p. 285-293.
16. De Vries, T., et al., *Guide to good prescribing: a practical manual*. 1994, Geneva: World Health Organization.
17. Diogene, E. and A. Figueras, *What public policies have been more effective in promoting rational prescription of drugs?* *J Epidemiol Community Health*, 2011. **65**(5): p. 387-8.
18. de Andrade, M., et al., *The Ethics of Pharma–Physician Relations in Pakistan: “When in Rome”*. *Ethics & Behavior*, 2018: p. 1-17.
19. Rosenbaum, P., Aureden, K., Cloughessy, M., Goss, L., Kassai, M., & Streed, S. A., *Guide to the Elimination of Multidrug-resistant Acinetobacter baumannii Transmission in Healthcare Settings*. *Elimination Guides*, 2010.
20. Guinovart, M.C., et al., *Obtaining antibiotics without prescription in Spain in 2014: even easier now than 6 years ago*. *Journal of Antimicrobial Chemotherapy*, 2015. **70**(4): p. 1270-1271.

## **Chapter 5 :**

# **Analyses of the registered fixed-dose combinations in Pakistan: a first step to improve the rational use of medicines**

**Farrukh Malik**

**Albert Figueras**

Submitted (Revised version after Referees comments)

Journal of Pharmaceutical Policy and Practice (*JoPPP*)

## 5.1 Abstract

**Background:** Fixed-dose combinations (FDCs) became a popular method to increase compliance among patients receiving multiple medications. While some FDCs are justified, many are irrational. A study was conducted to describe the approved FDCs in Pakistan, their rationality, and the reported sales of combinations that may have been discontinued in other countries.

**Methods:** Analyses of the largest sales database of Pakistan to identify the marketed FDCs and sales data. Also, the World Health Organization's Essential Medicines List (WEML) and the National Essential Medicines List of Pakistan (PEML) were compared to find differences in included FDCs. Multiple reference sources were used to identify rational, irrational, and discredited FDCs.

**Results:** The WEML and PEML included 33 and 27 FDCs, respectively, and 20 of them were common. There were 1259 FDCs present in the market with only 472, including at least one pharmaceutical active ingredient; almost 50% of these were considered 'irrational'. The analysis of the rationality, therapeutic advantages, and clinical relevance identified 50 FDCs that were either not justified or had been banned, withdrawn, or discredited in other countries but were still on the Pakistani market with the combined annual sales of more than 93 million units. Sixteen of these 50 FDCs had three or more active ingredients, with nearly 25 million annual units sold.

**Conclusions:** A critical analysis of the FDCs present in the pharmaceutical market of Pakistan, followed by actions of the drug authorities, should be the first step to improve the use of medicines and the quality of healthcare.

## 5.2 Introduction

In recent years more than one-third of the drug products introduced in the global pharmaceutical market was fixed dose combinations (FDCs).[1]. According to WHO, FDCs are justified in different situations. Namely, if they: (1) include active ingredients with complementary mechanisms of action, (2) decrease the occurrence of resistance in the case of antimicrobial agents, (3) increase the efficacy compared with their components being administered separately, (4) decrease the occurrence of toxicity, (5) increase patient compliance and/or (6) provide a dose of each of the different active ingredients that are appropriate for large groups of population [2].

In the assessment of a new FDC, it should be ensured that the pharmacokinetics of the drugs brought together as a mixture are roughly the same in terms of volume of distribution and peak plasma concentration than taken its components separately [3]. However, to show this, clinical and laboratory studies are required, and they are not always conducted. In real practice, many FDCs are marketed and promoted with the aim of trying to improve compliance among patients receiving multiple medications for various medical conditions.

A number of FDCs are considered irrational, and their prescription is not recommended for different reasons, such as exposure to unnecessary active ingredients, inability to titrate dosage according to individual patient requirements, or useless or superfluous additions (such as vitamins, minerals, etc.), or the increased risk of adverse drug reactions [3]. In the case of FDCs containing one or more antimicrobials, this could increase antimicrobial resistance [4]. Additionally, these irrational FDCs increase the presence of multiple confusing brands with similar but not equal composition, which could lead to unnoticed exposure to unnecessary drugs. Unfortunately, despite these challenges,



dangers, and disadvantages, they are included in some national essential medicines lists, [5, 6] but also readily prescribed [7].

Within this framework, the present study was planned to describe the FDCs present in the pharmaceutical market of Pakistan, their composition and rationality, as well as their consumption.

### **5.3 Methods**

Pakistan lacks an official central repository of registered medicines with data on prescription from all sources of healthcare delivery, such as primary care, private and public healthcare institutions, pharmacies, rural care clinics, prescriptions given out by lady health workers, etc. Most of the accessible data is available from the data sources of hospital pharmacies and prescription records. This, however, does not account for prescriptions from other places. Notwithstanding this, an estimated 80,000 products/brands (both single and FDCs) are believed to be registered with the Drug Regulatory Authority of Pakistan (DRAP). Thus, an indirect way to know the FDCs available in the country is by identifying all FDCs appearing in the sales files obtained from IQVIA Pakistan.

This study investigates the total number of registered drug molecules, the number of fixed-dose formulations, the presence of pharmaceutical and other ingredients in these combination products which are available for sale in the Pakistani pharmaceutical market.

#### **5.3.1 Consumption data source**

We used February 2018 data (covering last 12 months) from IQVIA Pakistan (former IMS Health - Pakistan) to identify FDCs sold in the country, as an indirect indicator of the

FDCs marketed in the country. Also, this data source provided information on sales of these products (from now on, 'consumption').

IQVIA data is a retail audit capturing sales directly from distributors to pharmacies, whole sellers, and retail pharmacies in small private hospitals. In the case of Pakistan, this database comprises of 85% actual sales, and 15% projected data for companies not sharing their distributor's data. In each sector, data is collected monthly to record direct sales from the manufacturer's designated distributors. This data is granulated into regional, city, and brick level for different distribution-channels [8]. The initial list categorizes the sales data according to brand names, molecular compositions along with their annual sales figures, but for study purposes, the analysis was kept for molecular compositions only.

### 5.3.2 Analysis of fixed-dose combinations

In the present study, an FDC was defined as any medical product containing more than one active ingredient (excluding excipients, conservatives, etc.), which are used to treat different ailments with the aims to improve patient compliance and attainment of the desired outcome.

In order to analyze the rationality of each FDC, first, the National Essential Medical List of Pakistan 2018 (PEML) was compared with the WHO's model list of essential medicines, 2017 (WEML), to develop an understanding of the similarities and differences for FDCs in both lists [9, 10].

A stepwise approach was taken to further analyze the total FDCs containing pharmaceutical and non-pharmaceutical ingredients. All products containing multivitamins or multivitamins + other active ingredients were then classified as 'undefined rationality' combinations products. The remaining combination products included only pharmaceutical ingredients and were then categorized as 'Pharmaceutical

FDCs'. They were classified according to the Anatomical Therapeutic Chemical classification (ATC) principles [11].

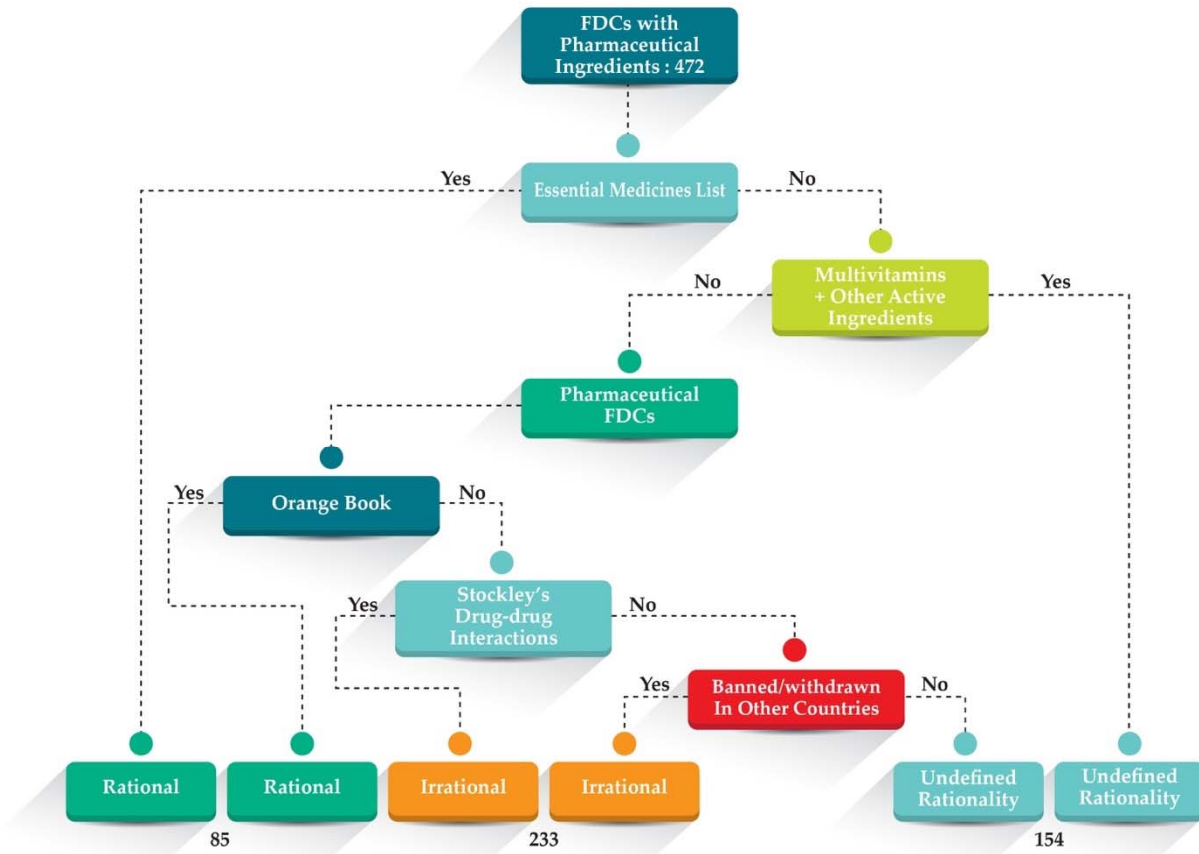
For all Pharmaceutical FDCs, the pharmacological appropriateness ('rationality') of the product was checked using different reference materials, mainly the FDA's *Orange Book*, [12], which enlists the recommended and approved FDCs along with approved presentations and doses. Those FDCs which were available in the Pakistani market but were not found as approved in FDA's Orange book were then evaluated for the possible drug-drug interactions of active ingredients in that FDC in Stockley's Drug Interaction book; [13] and then in the published literature for the appropriateness of their use in patients.

The FDCs list was also compared with other international lists of irrational or withdrawn drugs to determine whether any of these medications were still being sold in the Pakistani market [3, 14-16].

The intention was to identify published evidence enlisting any FDC as 'not rational', which could indicate that these must be at least considered for evaluation in Pakistan (

Figure 7).

Figure 7 : Flowchart explaining the research approach.



## 5.4 Results

The essential medicines list of WHO and Pakistan include 33 and 27 FDCs, respectively. There were 20 similar FDCs found in both lists, while the major differences were the absence of all six integrase inhibitors, an antiviral for the treatment of hepatitis C, a protease inhibitor, an antiparkinsonian, and an antiasthma product in the PEML. From the six antimalarial combinations in WEML, there were only three included in the PEML. Three therapeutic categories, including gastrointestinal, dermatological, and ophthalmological medicines, had four combinations in PEML while none in WEML. In the antibiotic category (J01), there were two additional beta-lactams in PEML (cloxacillin + ampicillin and imipenem + cilastatin).

The IQVIA Pakistan sales data included 15,993 products for which nearly three billion units were sold in the last 12 months. There were 1,429 single molecules; additionally, at least 1,259 different FDCs were present in the market and being sold.

Out of 1,259 FDCs, 787 were mixtures of herbal remedies, and 472 (37.5%) were categorized as pharmaceutical FDCs. According to the proposed classification, only 85 (18.0%) were clearly rational, while almost fifty percent (233) were found to be irrational (see

Figure 7). The remaining 154 FDCs (32.6%) contained at least one ingredient other than a pharmaceutical product and were categorized as FDCs with 'undefined' rationality. This analysis of the rationality, therapeutic advantages, and clinical relevance of the FDCs in

Pakistan allowed to identify 50 combinations that were either not justified or had been banned or withdrawn in other countries such as India, US, Australia, and the EU region.

Table 3 : Distribution of approved fixed dose combinations according to their ATC classification.

ATC	FDCs (with Pharmaceutical active ingredients only)	Rational FDCs: n (%)	Irrational FDCs: n (%)	FDCs with rationality undefined (Multivitamins/ Multivitamins + Allopathic) n (%)	Total number of approved fixed-dose formulations
A	173	27 (31.7)	66 (28.3)	80 (40.0)	503
B	64	05 (07.8)	05 (07.8)	54 (84.4)	75
C	22	18 (81.8)	03 (13.6)	01(04.5)	49
D	41	08 (19.5)	28 (68.3)	05(12.2)	168
H	36	12 (33.3)	19 (52.8)	05(13.9)	72
J	09	01 (11.1)	08 (88.9)	00	25
L	01	00	01 (100.0)	00	00
M	05	00	02 (40.0)	03(60.0)	43
N	20	02 (10.0)	17 (85.0)	01(05.0)	35
P	06	00	05 (83.3)	01(16.7)	13
R	42	04 (09.5)	36 (85.7)	02(04.8)	167
S	03	01 (33.3)	02 (66.7)	00	75
V	50	07 (14.0)	41 (82.0)	2(4.0)	34
	472	85	233	154	1,259

Data Source : IQVIA-Pakistan

More than one third (173) of the 472 FDCs belonged to the alimentary tract and metabolism category (A), and only 27 (15.6%) of them were clear rational. Also, this category has the highest number of FDCs with non-pharmaceutical active ingredients manifesting the huge current and future utilization potential. Other therapeutic classifications with the highest percentage of irrational combinations were Systemic Anti-Infectives (J), Respiratory system (R), Nervous system (N), and Dermatologicals (D) with 88.9%, 85.7%, 85.0%, and 68.3% respectively (

Table 3). It should be highlighted that in the case of anti-infective for systemic use (group J), 8 out of 9 FDCs were classified as irrational.

#### 5.4.1 Consumption of FDCs in Pakistan

Table 4 describes the annual sales units of unjustified FDCs in Pakistan, which amounted to more than 93 million units. The ten most consumed products (more than 81 million units, 87% of the total FDCs sales) included 7 FDCs for disorders of the alimentary tract (ATC group A), an analgesic, an anti-inflammatory and one FDC containing ampicillin and cloxacillin. The later (with 3.9 million units sold) should be highlighted because of the potential contribution of irrational FDC to antimicrobial resistance. Other FDCs containing antimicrobials were penicillin G + streptomycin (34,340 units), and amoxicillin + flucloxacillin (5,597 units). Sixteen of the 50 unjustified FDCs had three or more active pharmaceutical ingredients with nearly 25 million annual sales units. Alimentary tract and metabolism (A) have the highest number of FDCs with combined sales units of more than 71 million. Paracetamol was part of 27.3% (15) of these unjustified combinations, while 17 combinations had 3 or more active ingredients.



## 5.5 Discussion

This study found that 1,259 products containing fixed-dose combinations of active ingredients were being marketed in Pakistan, and only 7% of them could be considered clearly rational. Also, there was a high utilization of the irrational or unjustified FDCs, and at least 93 million units were sold over the 12 months studied. WHO has recently revised the AWaRe classification and included a list of "Non-recommended FDCs"; among those, ampicillin+cloxacillin alone (Table 4), had almost 4 million units sold in 2018 [17], a risk factor that could contribute to the increase of antimicrobial resistance.

Pakistan has multiple alternative medicine schools of thought; these include Yunani, Hakimi, Herbal, Homeopathic, Tibb, Chinese, etc. Sometimes these medicines are sold in pharmacies as well. There is no data to indicate the molecular composition of these drugs or their number of units sold. Further, there are no central registries or sources present for these kinds of medicines. The presence of counterfeit medicines, unregistered drugs, unannounced medications, and alternative therapies mean that the actual number of medications prescribed to the Pakistani population is much higher than the available data. This explains why, 62.5% of the 1,259 identified FDCs had been excluded from the present study, because they were mixtures of different herbal remedies and other non-pharmacological products, which, of course, can have clinical effects, which have not been appropriately studied. Higher rates of self-medication [18] in general, along with the common use of complementary health approach, especially in the case of a chronic condition has been found in the country [19], which seems a contributing factor in high use of fixed-dose combinations.

The availability of irrational or unjustified FDCs is a problem of many pharmaceutical markets and is one of the factors which contribute to the inappropriate use of medicines

and unnecessarily increase the risk of adverse drug reactions. In theory, this scenario should be easily avoidable with sound interventions from the Medicines Authorities [20].

The most reliable sales data used in this study provides information for 15,993 products for which nearly three billion units were sold during the study period, while approximately 80,000 products are believed to have already been registered by DRAP.

The WHO's 20th model essential medicines (WEML) list of 2017 contained 33 fixed-dose combinations. Based on this, many countries have developed their own lists of essential medicines, with additions or omissions based on the particular geographical and epidemiological profile. Pakistan released its updated list of essential medicines in October 2018, in collaboration with WHO, USAID, the DRAP, and medical professionals and authorities. The PEML contained 27 fixed-dose combinations with 20 exactly the same as in WEML. Looking at the differences, none of six integrase inhibitors, one antiviral for the treatment of hepatitis C, one protease inhibitor, one antiparkinson, and an antiasthmatic were listed in the PEML [9]. From the six antimalarial combinations in WEML, there were only three included in the PEML with an added combination of artesunate, sulphadoxine, and pyrimethamine. Four combinations in three therapeutic categories, including gastrointestinal medicines (aluminium hydroxide + magnesium trisilicate), dermatologicals (salicylic acid + betamethasone), and ophthalmologicals (polymyxin B + bacitracin zinc and tobramycin + dexamethasone) were present in PEML while none of those was listed in WEML. An additional two combinations of cloxacillin + ampicillin and imipenem + cilastatin were present only in PEML.

The presence of cloxacillin + ampicillin in the 2018 PEML does raise questions as this combination was found to be irrational and many countries have already discontinued its use [21] Both drugs in this FDC belong to the same class have the same mechanism of action & offer no synergistic effect [1] The highest number of formulations sold

(approximately 2 million units) contained 250mg of each drug and since both drugs are inactive against different bacteria using this specific strength can reduce efficacy for any particular infection and can add cost and potential adverse drug reactions [14]

According to the classification used in the present study (see methods), almost fifty percent of the pharmaceutical FDCs were irrational, while for about one third, the irrationality remained undefined due to one of the active ingredients as non-pharmaceutical. The health impact of such unverified combinations can be potentially significant, and it is also practically unknown. At the same time, the complicated nature of a disease, prescription patterns in comorbidities associated with each patient, the cumulative impact in terms of DALYs, and mortality would be challenging to calculate [22]. Merely 18% (85) of combinations were found to be clearly rational in the pharmaceutical market.

Alimentary tract drugs were the top sold medicines overall, and this popularity was reflected in the FDCs where more than one-third of the 472 pharmaceutical FDCs belonged to this category, and only 15.6% of them were clearly rational.

Rationality, therapeutic advantages, and clinical relevance analysis of all FDCs showed at least 50 FDCs that had been either not justified or banned or withdrawn in other countries but were still available and being sold on the Pakistani pharmaceutical market with the combined annual sales units of more than 93 million. Table 4 shows the high number of units sold of these unjustified banned or withdrawn FDCs. Paracetamol was found in 15 of these irrational FDCs, and among them, the mixture of paracetamol and tramadol was very popular (more than 11 million units sold in one year), an alert documented by different authors previously [20, 23].

Table 4: Highest Selling Unjustified Fixed-Dose Combination in Pakistan's Medicine Market.

S.No.	Active Ingredient	ATC	Therapeutic Category	Annual Sales Units 2018
1.	Paracetamol 500mg + Orphenadrine	A	Analgesic & Antipyretic	18,201,423
2.	Aluminium + Magnesium + Simeticone	A	Antacid	13,250,981
3.	Paracetamol + Tramadol	N	NSAIDs , Analgesic & Antipyretic	11,340,802
4.	Aluminium + Magnesium + Oxetacaine	A	Antacid	9,495,399
5.	Paracetamol 500mg + Caffeine	A	Analgesic & Antipyretic	8,582,800
6.	Omeprazole + Sodium Bicarbonate	A	Proton pump inhibitors	4,683,692
7.	Chlordiazepoxide + Clidinium	A	Antibacterial & Antispasmodic	4,493,188
8.	Glimepiride + Metformin	A	Antidiabetic	4,394,563
9.	Ampicillin + Cloxacillin	J	Antibiotic	3,916,020
10.	Diclofenac + Misoprostol	M	Analgesic	3,016,514
11.	Paracetamol + Scopolamine Butyl Hydroxide	A	NSAIDs, Anticholinergic	2,109,001
12.	Glimepiride + Pioglitazone	A	Antidiabetic	1,187,149
13.	Metformin + Pioglitazone	A	Antidiabetic	1,164,266
14.	Bromelains + Dimeticone + Metoclopramide + Pancreatin	A	Gastrointestinal agent	901,788
15.	Cinnarizine + Domperidone	A	Gastrointestinal agent	772,882
16.	Codeine + Ibuprofen	N	Opioids Analgesic	557,200
17.	Aluminium + Simeticone	A	Antacid	495,550
18.	Amlodipine + Olmesartan Medoxomil	C	Antihypertensive	455,284
19.	Fluphenazine + Nortriptyline	N	Anxiolytic & Antidepressant	451,375
20.	Mebeverine + Plantago Ovata	A	Spasmolytic agent	420,032
21.	Chondroitinsulfuric Acid + Glucosamine	M	Musculoskeletal	352,805
22.	Dicycloverine + Simeticone	A	Antispasmodic	325,777
23.	Fluoxetine + Olanzapine	N	Antidepressant	321,004
24.	Domperidone + Esomeprazole	A	Gastrointestinal Agent	315,553
25.	Flupentixol + Melitracen	N	Anxiolytic & Antidepressant	289,628
26.	Other <sup>1</sup>			1,607,854

<sup>1</sup> Among the "Other" category, there were 03 FDC containing at least one antimicrobial: penicillin g + streptomycin (34,330 units), amoxicillin + flucloxacillin (5,497 units), and kanamycin+ penicillin G (2,139 units)

Data source: IQVIA-Pakistan

The annual growth of the sales units is almost ten percent showing the magnanimity of drug utilization and its challenges. While the high rate of FDC utilizations in general and irrational FDCs, in particular, is disturbing, even more, worrying is the lack of intellectual inquiry and cross-verification among physicians, who continue to prescribe such medications without assessing the rationality of the drug combination [24]. Multivitamins are heavily prescribed, with mostly mentioning brand names on the prescriptions [25]. Vitamins are indicated in the case of nourishing problems and vitamin deficit, but the products to be prescribed should be selected carefully according to the specific hypovitaminosis, and no clear evidence exists for most of these multivitamin mixtures including low or very low dosages.

### 5.5.1 A Rising Trend of Fixed Dose Combination Prescribing Pattern

As prescribers in Pakistan continue to prescribe multiple drugs, fixed-dose combinations gain broader appeal and acceptance both amongst healthcare professionals and the patients. A *two in one* pill that could help deal with more than one situation is popular among patients. Due to limited post-marketing research and drug utilization research carried out locally, there is a heavy reliance on the information provided by the pharmaceutical manufacturers and which may not be relevant to the local setting at times. The overall lack of research culture amongst healthcare professionals further maximizes the ignorance levels in healthcare settings, and the potential damage due to this behaviour is devastating. As a fertile market environment for pharmaceutical companies to dish out new combinations, Pakistan provides a rich opportunity to bring new drugs in the market, especially in a fixed-dose combination [26].

With improving access to medicines and the global rise in the prevalence of non-communicable and chronic diseases, there is an incremental rise in the consumption of

both preventive and therapeutic categories of medications, which are bringing newer challenges in the case of fixed-dose combinations.

Although to address the kind of problems raised in this study are not easy because of the popularity of some of these products among users and prescribers, and also potential pressure from local manufacturers, some recommendations to Health Authorities could be made. For example, the possibility to award marketing authorization only for the FDCs having an evidence-based therapeutic justification and enforce strict controls on their prescription. Also, healthcare professionals should be made aware of the irrational FDCs and the morbidity and mortality risk associated with it. The strengthening of the National Pharmacovigilance System of Pakistan could include identifying risks associated with the consumption of these irrational products as one of its priorities. Finally, patients and the general public must be educated about the risks associated with using unnecessary medications.

The data resources used for this study were gathered for market analysis purposes only and included data based on the number of units sold. It is not confirmed if, for a particular molecule or product to be included in these lists, if there was any cut-off point in the number of units sold. The data does not indicate or present the actual number of molecules that may be registered with the Drug Regulatory Authority of Pakistan. However, for an initial exploratory study, the data source is sufficient due to its accuracy. Such a method has been used in other studies as well [27]. In any case, the consumption estimations given in our study were in the worst-case underestimations.

## **5.6 Conclusion**

In summary, analyses of the total pharmaceutical market data showed that almost fifty per cent of the FDCs with active pharmaceutical ingredients only are believed to be irrational, with at least 50 unjustified products still available in the Pakistani market,

which have either been banned or withdrawn in other countries. The 2018 PEML also included a questionable combination of cloxacillin + ampicillin, which seemed very popular (almost 4 million units sold annually). An in-depth analysis of the pharmaceutical market in the country is needed to identify urgent actions required to mitigate the flow of irrational FDCs. At the same time, studies conducted by the National Pharmacovigilance System could help to identify preventable risks associated with the use of these irrational products.



## 5.7 References

1. Poudel, A., et al., *Irrational fixed dose combinations in Nepal: need for intervention*. Kathmandu Univ Med J (KUMJ), 2008. **6**(23): p. 399-405.
2. World Health Organisation. WHO. *WHO Expert Committee on Specifications for Pharmaceutical Preparations : thirty-ninth report*. Geneva. WHO technical report series ; 929 2005; Available from: <http://www.who.int/iris/handle/10665/43157> (accessed on).
3. Raju, K., A. Elumalai, and E. Sridhar, *Irrational Drug Combinations*. International Journal of Experimental Pharmacology, 2013. **3**(2): p. 52-56.
4. Joelsing, F., *India's antibiotic combinations thwart efforts to curb drug resistance, say researchers*. BMJ, 2018. **360**: p. k560.
5. Rico-Alba, I. and A. Figueras, *The fuzzy line between needs, coverage, and excess in the Mexican Formulary List: an example of qualitative market width analysis*. Eur J Clin Pharmacol, 2013. **69**(4): p. 949-56.
6. Khjauria, V., et al., *Profile of Adverse Drug Reactions with Fixed Dose Combinations: How Big is the Problem*. JK Science, 2015.
7. Sarkar, C. and B. Das, *Prescribing trend of fixed-dose drug combinations in a tertiary hospital in Nepal*. Journal of Institute of Medicine, 2007. **22**.
8. IQVIA/IMS. *Gain the most accurate and reliable view of market demand*. Available from: <https://www.iqvia.com/locations/united-states/commercial-operations/essential-information/prescription-information> (accessed on 4 July 2019).
9. Drug Regulatory Authority, P. *National Essential Medicines List NEML 2018*. 2018; Available from: <http://www.dra.gov.pk/Home/PharmacyServices> (accessed on 4 July 2019).
10. World Health Organisation. WHO. *WHO Model Lists of Essential Medicines*. Essential medicines and health products 2017; Available from: <https://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf?ua=1> (accessed on 4 July 2019).
11. WHO. Collaborating Centre for Drug Statistics Methodology, *Guidelines for ATC classification and DDD assignment 2019*. 2018.



12. US Food and Drug Administration, F., *Orange Book Data Files. Electronic Resource.* 2018.
13. Van Mil, J.W.F., *Stockley's drug interactions 11th edition.* Vol. 38. 2016.
14. Gautam, C.S. and S. Aditya, *Editorial - Irrational drug combinations: Need to sensitize undergraduates.* Indian Journal of Pharmacology, 2006. **38**(3): p. 169-70.
15. Siramshetty, V.B., et al., *WITHDRAWN—a resource for withdrawn and discontinued drugs.* Nucleic Acids Research, 2015. **44**(D1): p. D1080–D1086.
16. National Health Portal, N. *Complete list of 344 drugs banned by the Ministry of Health Family welfare.* 2016; Available from: [https://www.nhp.gov.in/Complete-list-of-344-drugs-banned-by-the-Ministry-of-Health-Family-welfare\\_pg](https://www.nhp.gov.in/Complete-list-of-344-drugs-banned-by-the-Ministry-of-Health-Family-welfare_pg) (accessed on 4 July 2019).
17. World Health Organisation. *WHO AWaRe classification of antibiotics for evaluation and monitoring of use.* 2019; Available from: [https://www.who.int/medicines/news/2019/WHO\\_releases2019AWaRe\\_classification\\_antibiotics/en/](https://www.who.int/medicines/news/2019/WHO_releases2019AWaRe_classification_antibiotics/en/) (accessed on 4 July 2019).
18. Aqeel, T., et al., *Prevalence of Self-Medication among Urban and Rural Population of Islamabad, Pakistan.* Tropical Journal of Pharmaceutical Research, 2014. **13**(4).
19. Ayaz, S., et al., *The use of complementary health approaches among patients with knee osteoarthritis in Pakistan: A hospital based survey.* The Egyptian Rheumatologist, 2016. **38**(2): p. 111-116.
20. McGettigan, P., et al., *Use of Fixed Dose Combination (FDC) Drugs in India: Central Regulatory Approval and Sales of FDCs Containing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Metformin, or Psychotropic Drugs.* PLoS Med, 2015. **12**(5): p. e1001826; discussion e1001826.
21. Poudel, A., S. Palaian, and M. Izham, *Use of ampicillin / cloxacillin combination in Nepal: need for Intervention.* Journal of Gandaki Medical College – Nepal, 2008. **1**(2): p. 70-72.
22. Ofori-Asenso, R. and A.A. Agyeman, *Irrational Use of Medicines-A Summary of Key Concepts.* Pharmacy (Basel), 2016. **4**(4).
23. Gautam, C.S. and L. Saha, *Fixed dose drug combinations (FDCs): rational or irrational: a view point.* Br J Clin Pharmacol, 2008. **65**(5): p. 795-796.
24. Das, N., et al., *Prescribing practices of consultants at Karachi, Pakistan.* J Pak Med Assoc, 2001. **51**(2): p. 74-7.

25. Raza, U.A., et al., *Prescription patterns of general practitioners in peshawar, pakistan*. Pak J Med Sci, 2014. **30**(3): p. 462-5.
26. Aamir, A. and K. Zaman, *Review of Pakistan Pharmaceutical Industry: SWOT Analysis*. 2011. **1**(1): p. 114-117.
27. Wirtz, V.J., et al., *Use of antibacterial fixed-dose combinations in the private sector in eight Latin American Countries between 1999 and 2009*. Trop Med Int Health, 2013. **18**(4): p. 416-25.

## **Chapter 6 : Discussion**

The different studies included in the present thesis allowed us to analyze the medicines market in Pakistan, with a special focus on antimicrobials. Among the main results observed in these three parallel approaches, it could be highlighted that the antimicrobial market in Pakistan had at least 73 single and combination antimicrobial active ingredients, with the market offering of 1869 brands and 4648 presentations when the study was conducted. Beyond the figures, the astonishing fact was that more than half of these active ingredients, classified as 'Watch' antibiotics, offered over two-thirds of all brands.

In a second and more detailed analysis of the Pakistan market, it was found that there were 472 fixed-dose combinations, but only 18% of them had enough evidence to justify its marketing and use. Once again, beyond the figures, it should be highlighted that 50 of these FDCs (i.e., almost 10% of those marketed) had been already banned or withdrawn in other countries. We found that more than 93 million units of these 50 FDCs were sold in the country in the twelve months period (March 2017 – February 2018) and that almost 4 million units of these FDCs contained antimicrobials, a risk factor that could contribute to the increase of antimicrobial resistance.

To complement our approach about the market of antimicrobials in the country, the third study analyzed the consumption of two different therapeutic subgroups, that of cephalosporins and that of fluoroquinolones. These two groups were chosen because of their high consumption in many countries and also because all quinolones and many cephalosporins belong to the "Watch" group. Indeed, sales analysis of cephalosporin and fluoroquinolone antibiotics in Pakistan during five years showed a combined increase of 1.8598 DID, i.e., in 2018, an additional 386,000 patients were receiving one of these antimicrobials every day in comparison to the consumption in 2014.

## 6.1 Putting the results into context

It is quite challenging to find the accurate statistics on medicines' expenditure from the overall health expenses of patients in Pakistan, but World Health Organization estimated the total pharmaceutical expenditure in low-and lower-middle-income countries is approximately 30%, and a significant portion of the health spending is used in buying medicines in these countries [1]. Almost one-third of the total health expenditure in Pakistan is estimated to be for public health expenditures [2], while the total pharmaceutical sales as a percentage of healthcare expenditure for Pakistan is nearly 35% [3].

### 6.1.1 Pharmaceutical Industry in Pakistan

In order to comprehend the medicines market in Pakistan, it is essential to understand the pharmaceutical industry of the country. The number of pharmaceutical manufacturing units in the country has grown from 304 in 1999 to 789 in 2019, with at least 648 active pharmaceutical manufacturers and only 22 multinational companies, also called MNCs [4].

Also, the top 100 companies in revenues dictate the market as they control almost 97% of the market. The Pakistani pharmaceutical market is best described as a market of branded generics that dominate the market share as originator medicines are only produced by MNCs. More than 80% of medicines are manufactured within the country, and the top 50 pharmaceutical companies have a market share of 89%, which goes to 97% for the top 100 [5].

Pakistan is one of the 21 countries categorized a "pharmaemerging" due to its huge growth potential [6]. The branded generic market competes with pricing as well as branding. Although the sector is fully regulated by the state at a federal level through the drug regulatory authority of Pakistan (DRAP), some functions, including regulation of

the wholesale and retail markets, inspection, and laboratory testing through quality control boards, are performed at a provincial level.

The findings suggest one key action to be taken is to reconsider the available products according to the best evidence, followed by an evaluation of their risks and benefits. A benchmark may be sought with other regulatory bodies around the world for reference. Forming a specialized commission may be a useful approach in setting up stepwise plans to define an evidence-based product strategy, focusing public health at large.

### 6.1.2 The paradox of a big market width and shortage of medicines

Developing countries like Pakistan can have a dilemma while explaining medicines related problems with big market width and shortages, causing limited access to medicines at the same time. As the results of the three studies earlier discussed clearly show that there is an excess market width of antimicrobials with two top-selling classes having an enormous number of presentations for some, the concept may sound bizarre.

## 6.2 Adopting drug utilization studies methodology in Pakistan

Drug utilization studies (DUS) are a helpful tool to know and understand how medicines are being used at different levels of the therapeutic chain in a given country, and also to have a quantitative and qualitative approach to that consumption. The studies presented in this thesis are just three examples of what could be done in the country systematically and with the most relevant therapeutic groups, beyond antimicrobials.

Despite the existence of different data sources useful to conduct DUS at different levels, electronic databases provide interesting information which allows us to analyze consumption at the patient level; and combining medicines utilization data with other clinical information adds an interesting dimension to these studies[7].

The introduction of a universal prescription recording system for all inpatients and outpatients in Pakistan, to generate the local medicine use data and to know the degree of adherence to local clinical guidelines, should be considered by health authorities. Despite not being the panacea and having different limitations, electronic medical records could be highly useful in the country.

In the specific case of antimicrobials, amidst the present Global awareness due to the growing antimicrobial resistance and the lack of new antimicrobials able to face multi-resistant strains, publishing drug utilization data by using antimicrobial consumption tools based on WHO standards (GLASS initiative) as well as DUS at different healthcare levels as part of national and local stewardship programs, could really help to identify misuse problems and to design campaigns to address them. In these analyses, using the AWaRe classification, ATC classification system, and the defined daily doses (DDD) methodologies could help to reflect national, provincial, and local consumption trends as well as regional differences. Additionally, by adopting these methodologies, Pakistan will be using international standard measures, which could allow comparing local results at the international level. This will bring more transparency into the system and will generate discussion at both academic and general levels, thus increasing awareness among prescribers, dispensers, patients, authorities, and the general public.

### **6.3 Available medicines as a first step to rationalize the consumption of medicines**

Different studies conducted since the introduction of the concept of the rational use of medicines in the 80s have shown the benefits of limiting the number of medicines available in a country or hospitals, the usefulness of drug formularies, and therapeutic guidelines [8]. The value of the Essential Medicines List proposed by the World Health

Organization and periodically reviewed and updated by a WHO Expert Committee since 1985, is also well recognized [9].

Pakistan also has a National Essential Medicines List (NEML) since 1994 [10]. The NEML (as it is the WHO-EML) is only a guide on the basic medicines which should be available in the country to solve the most prevalent healthcare problems. However, NEML, perhaps accompanied by a national formulary that addresses these relevant healthcare problems and clinical guidelines, which are clear, based on the last available evidence, periodically updated and free of conflicts of interests, are necessary tools to improve how medicines are being prescribed and used in the country.

More awareness about NEML could improve the prescribing practices, thus help promote the rational use of medicines in the country; otherwise, it is just another totemic publication sitting in the archives of the health system.

#### **6.4 From the volume-based market to value-based market**

National drug policy should be based on legislation, selection of drugs, registration (what to register and what not to register), quality, procurement, distribution, education, training, and availability of the updated information derived from evidence-based research if not local then international. Regarding the policy on registration and renewal, the field assessment of drug utilization must be considered to aptly comprehend the patient needs.

Both Scientific and real-world evidence based regulatory decisions are needed to control what product needs to go in, what product needs to stay in, every product needs to be monitored irrespective of its therapeutic and efficacy profile, and more importantly what more of the same already present in the pharmaceutical market is Not necessary to promote the rational use.



Hopefully, the forthcoming National Medicines Policy in Pakistan will be useful to strengthen how medicines are used in the country at all levels of the value chain, beginning with the medicines authorization process and ending with the actual utilization of these medicines by patients. A good prescription process with little influences from marketing promotion, following proper guidelines, lowering the rates of dispensing without prescription in pharmacies and empowering citizens for responsible self-medication, all covered by a robust national surveillance program which uses different pharmacovigilance tools for the early detection of any problem related with adverse drug reactions of these marketed medicines.

## **6.5 Limitations of Using Sales Data for Analysis**

Like any methodology, drug utilization studies based on sales data at a national level have several limitations that should be taken into account before extrapolating them.

Of course, the best approach to know how medicines are being used (or even if a specific patient has actually taken a medicine) consists of looking at each patient individually. With a country perspective, this is impossible, so other methods are used as a proxy to that individual level, and “consumption data” such as those presented by IQVIA (used in our studies), are among the most reliable, because of the standard methodology used by the company in the different countries and also their long-standing experience in doing so. In fact, IQVIA data (formerly IMS), have been the basis of several studies published in well-renowned journals.

Updated pharmaceutical sales data is one of the most authentic resources of drug sales information and is a reliable tool to assess the gross medicine utilization and the trends therein, especially in the presence of other incomplete, unreliable, and sometimes wholly absent sources.

However, the major limitation using sales data analysis is that while it does show the number of units sold (indicating prescriptions or direct buying behaviour), it fails to highlight the reasons for any trends that are found. Another primary limitation is that the data source did not give any information on the products which were approved but had no recorded sales.

The sales data, do not necessarily represent the actual consumption by patients and is not representative of hospital usage for inpatients and also does not explain the individual over the counter buying for self-medication. Also, the pharmaceutical sales data alone cannot give any indication about unauthorized or unapproved medicines, fake drugs, and drugs from alternative medicine.

Again, this means that the sales data may provide an idea about the trends of medicines uses in the market, but fail to deliberate its reasons or rationale. This poses a policy challenge, especially in markets that are not tightly regulated.

Another point to consider is while sales data may show a high number of sales, this does not automatically equate to access to medicines in all areas where the pharmaceutical market operates. Only locality-based sales data would give insights into the distribution of drugs, which would indicate access based on population statistics and local healthcare needs.

In the case of antibiotics, sales data has the limitation to ascertain if the high incidence of prescribing is due to physicians' usual practice, a high rate of infectious disease rates, or due to inadequate access of care for patients leading to complications before medical attention or care is given, thus requiring more antibiotics. In the case of developing countries like Pakistan, all three can be possible contributors. However, none can be pinpointed unless there is evidence to correlate.

To assess the full situation; therefore, market sales data must be analysed in conjunction with other data and factors that help determine the causes of irrational drug prescription patterns.

Despite this, in our opinion, the data used in the three studies included in the present thesis, are the best available ones at the country level in Pakistan in the present moment.

## **6.6 Recommendations to Counter Irrational Drug Prescription**

### **Patterns**

Over time, many recommendations have been put forward by international regulatory organizations to counter the growing menace of irrational medicine and antibiotics prescription. However, the one size fits all approach is not able to address the unique factors that contribute toward the phenomenon itself.

It is, therefore, important that national regulatory authorities develop a *GLOCAL* approach towards pharmaceutical regulation. The guidelines can be aligned to the international standards, while modified to ensure local factors are addressed adequately.

Below are some short and long term recommendations for countering irrational drug prescription patterns on a national level.

#### **6.6.1 Short Term Targeted Approach**

1. Awareness and education of medical professionals about the growing phenomenon, its impact and ways to mitigate it
2. Mandatory training courses as part of maintaining licensure to help physicians review new developments and content in the pharmaceutical industry
3. Early-on problem-based training of medical professionals in rational prescribing during training and educational years

4. Educational resources independent of pharmaceutical companies' approach; national documents aimed and providing quality, unbiased, academic, evidence-based and internationally compliant information on medicines
5. Managerial interventions where hospitals and healthcare systems closely monitor prescribing practices as part of quality controls and audits, and give feedback, thus ensuring compliance with policies [11].
6. Public awareness and education about the harmful effects of irrational drug usage.

### 6.6.2 Long Term System-Based Approach

1. Regular monitoring of medicines use through an assigned national body bearing strong regulatory and legal powers
2. Identifying factors that determine or influence inappropriate prescribing behaviour
3. Developing essential lists tailored to locality (provincial or district) needs and using these for decisions pertaining to the registration of new drugs in the market.
4. District-based therapeutic committees monitoring rational use of drugs in the region and hospitals
5. Developing wise lists: The lists were first introduced in Stockholm, stating that "drug recommendations should be issued in one version for the whole region by respected drug experts to enhance the quality of care" [12]. The wise list was developed based on seven key elemental concepts:
  - Independent drug expert organization with network chooses and recommends the wise list of drugs
  - One concise, wise list should be developed for both ambulatory and hospital care. The drugs would be added or removed depending on the complexity of the care institution
  - Strict criteria for drug recommendation with rational

- Promotion of wise list as the most authentic source of information for medicines to be prescribed
  - Targeted wise list editions based on the locations they are deployed, e.g., primary care, public or private hospitals, etc.
  - Feedback on prescription patterns to prescribers and advice on improving behaviour and practice
  - Leadership buy-in and commitment [12]
6. Develop measures for effective collaboration between healthcare professionals, patients, and pharmacies
  7. Laws and regulations creating stricter controls over the launch and release of new drugs into the market
  8. Creating higher registration prices to deter unnecessary and repetitive molecules and generic brand registration. Alongside, creating a condition for submitting a strong case against any generic brand that is already present in the market and rejecting any combination that does not justify its *benefit* in the market
  9. Creating incentives for physicians for the *most prudent prescription of medications with good patient outcomes*. Hospitals can be ranked for quality based on their prescribing practices including quality medicines with a strong rationale
  10. Limiting the dispensing of certain medications in primary care centres to counter unnecessary antibiotic use [11]. However, one must consider locations where primary care centres may be the only source of healthcare in rural areas, such as rural parts of Pakistan
  11. Pharmacies forced to provide generic substitution of lower-priced drugs when presented with a prescription that contains a higher cost brand. This will force the competition to create high-quality medicines at lower prices, and prevent the registration of new brands of the same generic in the market.

### 6.6.3 Regional Recommendations with other countries

1. Creating alliances and regulatory bodies that cover regions and countries with similar challenges in healthcare and pharmaceutical regulation, such as developing countries
2. Building think tanks that agree on ethical and moral frameworks on rational prescribing and give voice and weight to the growing challenge
3. Regional think tanks to review the performance of national regulatory bodies and question the presence of irrational drugs in the market. Countries with similar problems coming together to identify strategies that helped address challenges contributing toward irrational prescription behaviour
4. Regional bans on importing or bringing medicines that have been banned in the country from outside. Ensuring these bans do not inadvertently harm patient population who may need the drug and do not have a suitable substitute available in the market
5. Creating an antibiotic watch group which would collect reports from different countries and correlate findings on antibiotic use, misuse, irrational prescription behaviour and formulate strategies to counter them

It should be highlighted at this point that the Ministry of Health of Pakistan is currently finishing the last draft of the new National Medicines Policy, which probably will be published by 2020. Hopefully, some of these proposals will be addressed by this National policy.

## 6.7 References

1. Kaplan, W. and C. Mathers. *The World Medicines Situation 2011*. 2011; 3:[Available from: <http://apps.who.int/medicinedocs/documents/s20054en/s20054en.pdf?ua=1>.
2. World Bank. *Health Expenditure*. 2016 11 September 2019]; Available from: <http://data.worldbank.org/indicator/all>
3. Business Monitor International. *BMI Pharmaceutical and Healthcare Database*. 2016 11 Septmeber 2019]; Available from: <https://bmo.bmiresearch.com/data/datatool>
4. IQVIA, 2019.
5. Dawani, K. and A. Sayeed, *Pakistan's pharmaceutical sector: issues of pricing, procurement and the quality of medicines*, in ACE SOAS Consortium Working Paper 012. 2019, Collective for Social Science Research, Karachi: Karachi.
6. QuintilesIMS, I. *Outlook for Global Use of Medicines through 2021*. 2016 11 September 2019]; Available from: [http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/outlook\\_for\\_global\\_medicines\\_through\\_2021](http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/outlook_for_global_medicines_through_2021).
7. Cook, M.N., *Estimating national drug consumption using data at different points in the pharmaceutical supply chain*. *Pharmacoepidemiology and Drug Safety*, 2006. **15**(10): p. 754-757.
8. Diogene, E. and A. Figueras, *What public policies have been more effective in promoting rational prescription of drugs?* *J Epidemiol Community Health*, 2011. **65**(5): p. 387-8.
9. World Health Organisation. *The Selection of Essential Medicines WHO Policy Perspectives on Medicines*, No. 4 2002 05 October 2019]; Available from: <https://apps.who.int/medicinedocs/en/d/Js2296e/>.
10. Arshad, S., et al., *Assessment of Essential Drug List in Lahore Retail Pharmacies* *Journal of Pharmacy and Alternative Medicine* 2016. **10**.
11. Ofori-Asenso, R. and A.A. Agyeman, *Irrational Use of Medicines-A Summary of Key Concepts*. *Pharmacy (Basel)*, 2016. **4**(4).
12. Gustafsson, L.L., et al., *The 'wise list' - a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm*. *Basic Clin Pharmacol Toxicol*, 2011. **108**(4): p. 224-33.

## **Chapter 7 : Conclusions**



1. In Pakistan, an analysis of the pharmaceutical market focusing on antimicrobials has shown a high ratio of Brands/Active ingredients, which seems wider than apparently needed. This is especially relevant in the case of **36** 'Watch' antimicrobials, which has **1271** brands available in the market.
2. The combined consumption of both cephalosporin and fluoroquinolones in 2018 increased by **386000** more patients receiving these drugs each day in Pakistan.
3. The market analysis conducted in this project found **472** FDCs, and **only 18%** of them were rational or justified from the pharmacological & therapeutical point of view.
4. More than **10%** of the FDCs had been withdrawn in other countries, and despite the established *connaisance*, at least **93 million** units of these FDCs were consumed in the country each year.
5. Market analysis and consumption analysis are important studies that should be included as part of the AM stewardship in any country.
6. A comprehensive review of Pakistan's medicine market is needed for the appropriate adequation of the market to the available evidence.
7. The forthcoming National Medicines Policy document can be an excellent opportunity to address some of the problems identified in the present thesis.

## **Too much & too little about medicines in Pakistan**

Too much of any authorized drug (active ingredient) in the body causes toxicity of its chosen type, on a particular site adopting a unique pathway potentially causing harm that may or may not be avoided, detected, and treated in the shortest possible time.

--

Too little of any authorized drug (active ingredient) in the body compared to its recommended dose and duration of usage is incapable of giving the desired effects as anticipated by the prescriber and the ailing patient.

--

Too many registered products and presentations (>80,000) compared to the actual numbers currently being marketed (<20,000) raises questions

--

Too little of surveillance on what's happening with the pharmaceutical market width is worrying

--

Too many products/brands and presentations of any medicine are likely to cause confusion and uncertainty with the prescriber, dispenser, and consumer

--

Too little producer (or MAH) independent information limits the practices of good prescribing behavior

--

Too many antibiotics presentations, especially Cephalosporins and Quinolones from the 'Watch' group of AwARe, will contribute to irrational prescribing and yet antibiotic resistance

--

Too little knowledge of the national and regional antibiotic resistance patterns limits choosing the best medicines and the respective interventions to control the irrational use.

--

Too many unwanted and unnecessary fixed-dose combinations can potentially raise the adverse drug reaction index on Antimicrobial resistance of the whole patient population

--

Too little of regulatory control in accessing otherwise prescription-only medicines as over the counter promotes self-medication and irrational use

--

Too much of a *Laissez-faire* strategy will complicate things further and make the problem chronic.