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Ganga, Nelisa Paidamwoyo

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A MEDICINE UTILIZATION STUDY FOR VIRAL BRONCHITIS IN PRIMARY HEALTHCARE SETTINGS IN JOHANNESBURG

Nelisa Paidamwoyo Ganga

A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Pharmacy

Johannesburg, 2021

DECLARATION

I Nelisa Paidamwoyo Ganga declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____

(Signature of candidate)

_4th_day of_November_2021_ in the Department of Pharmacy and Pharmacology

DEDICATION

I dedicate this dissertation to my father Mr. Donald Ganga, my mother Professor Emily Ganga, my older brother Mr. Brett Ganga, my sister-in-law Mrs. Tendai Ganga, my older brother Mr. Warren Ganga, my younger brother Mr. Donald Ganga Junior, and the rest of the Ganga family. Thank you very much for being there for me always and for encouraging me to work extremely hard. I remember you motivated me recurrently with the quote by Sir Nelson Rolihlahla Mandela which says, "Education is the most powerful weapon which you can use to change the world." In addition, you consistently advised me that I must be creative, set goals and strive for academic excellence during my postgraduate journey. Furthermore, you inspired me invariably by saying that the secret of getting ahead, is getting started. Moreover, you always encouraged me with the quote by Sir Vince Lombardi which says, "Perfection is not attainable, but if we chase perfection, we can catch excellence."

Thank you for advising me that I must set principles for myself, be humble, maintain my dignity and integrity wherever I go, listen to advice, and accept corrections. I remember the two proverbs you usually stated which are, ‘‘whoever loves discipline, loves knowledge but he who hates reproof is mindless,’’ and ‘‘where pride comes, there comes disgrace, but humility brings wisdom.’’ Additionally, you always encouraged me to manage my time wisely by saying that piling up too many tomorrows, will leave me with a bunch of empty yesterdays. Thank you for motivating me with the quote by Sir William Shakespeare which says, ‘‘Be not afraid of greatness, some are born great, some achieve greatness, and some have greatness thrust upon them.’’ My dear Ganga family, your love and support has made this postgraduate endeavour a success. Words alone cannot fully express how grateful I am to you all. Thank you very much indeed my loved ones.

PUBLICATIONS ARISING FROM THIS RESEARCH PROJECT

Paper 1: The therapeutic applications of cough medicines in respiratory diseases

The student is the primary author and corresponding author of the article (Appendix A)

Status: Accepted for publication by the International Journal of Pharmaceutical and Phytopharmacological Research (IJPPR) (Appendix B) and published on the 4th of June 2021.

Researcher	Name	Signature	Date
1.Student/Primary author	Nelisa Paidamwoyo Ganga		04/11/2021
2.Main supervisor	Dr Neelaveni Padayachee		04/11/2021
Comments by main supervisor			

ABSTRACT

Viral bronchitis or acute bronchitis is an infection of the airways which is mostly of viral origin and occurs mainly in the winter months. It affects 6% of children, 5% of the adult population annually and it tends to affect women more than men. Little is known about the level of adherence to guidelines in the treatment of acute bronchitis in South African primary care. Several medicines such as antibiotics, corticosteroids, and opioids are being used routinely in practice to treat acute bronchitis, although, several guidelines do not recommend them.

This study aimed to assess prescribing patterns, dispensing practices, medicine utilization and legal aspects in the treatment of acute bronchitis in both public and private primary healthcare settings in Johannesburg. This study was a non-experimental drug utilization study that included prescriptions from 181 patient visits and dispensed medicines from 378 patient visits by standardized patients. These 559 patient visits were made to 186 private doctors and 73 public clinics in Johannesburg. Data was captured on REDCap and analysed using STATA software version 15 for windows.

The research findings show a total of 1789 medicines from this study, with the maximum number of drugs in the public sector being four, while in the private sector the maximum was seven. Combination medicines or fixed-dose combinations were prescribed and dispensed most frequently (29.0%; n=520), followed by antibiotics (22.5%; 402) and thirdly corticosteroids (12.6%; 226). Of all the 559 patient visits, 29.34% (n=164) had drug-drug interactions.

Based on the label requirements of the Medicines and Related Substances Control Act 101 of 1965, five labels were fully compliant in the private sector, while two labels were fully compliant in the public sector. For labels on original containers of medicines, the study found that there were no statistically significant differences ($p > 0.05$) between dispensing doctors in the private sector and Primary Healthcare (PHC) nurses in the public sector in terms of labelling for the name of patient ($p = 0.199$) and reference number ($p = 0.227$), where dispensing doctors complied better than the PHC nurses. For labels of dispensed medicines that had been repacked, the study found that there were no statistically significant differences ($p > 0.05$) between dispensing doctors in the private sector and PHC nurses in the public sector in terms of labelling for the batch number ($p = 0.397$), reference number ($p = 0.397$) and expiry date ($p = 0.836$).

As per regulation 33 of the Medicines and Related Substances Control Act 101 of 1965 which sets out the legislation for a prescription, none of the 181 prescriptions was fully compliant. With regard, to the dispensing and prescribing practices in this study, there was an overuse of combination medicines, underuse of antivirals and polypharmacy was a major problem. It is not clear why antibiotics and corticosteroids were used so frequently, especially given that there is no evidence base for the prescribing or dispensing of these medicines. The results from this study highlight areas in practice needing immediate attention such as non-adherence to evidence-based treatment guidelines, polypharmacy, drug-drug interactions, and non-compliance to legislation. Further research in drug utilization is needed before strategies may be developed to improve dispensing and prescribing practices in primary care.

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Secondly, l would like to thank my main supervisor Dr. Neelaveni Padayachee and my co-supervisor Dr. Deanne Johnston. No amount, of words, can be enough to thank my supervisors for helping me with my research project. The help my supervisors gave me is priceless. My supervisors worked tirelessly hard to make this dissertation a success despite their heavy workload. They have been committed, supportive and amazing throughout my postgraduate journey. They mentored and nurtured me into a virtuous pharmacist who is extremely passionate about research. In addition, I exceedingly cherish the enthusiasm and remarkable zeal for the pharmacy profession that they have instilled in me. I highly appreciate their leadership and contributions to my project. The quality of this dissertation reflects the passion, dedication, commitment, and technical expertise of Dr. Padayachee and Dr. Johnston who critically reviewed this dissertation before submission.

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

This chapter aims to provide the background, epidemiology, definition, aetiology, pathophysiology, diagnosis, and treatment of viral bronchitis. Additionally, the rationale for using each medicine, as outlined by the evidence-based clinical practice guidelines is explained. Furthermore, the dangers involved with irrational medicine use for acute bronchitis are explained. This chapter concludes with the aim and objectives of this study.

1.2 Background and epidemiology of acute bronchitis

About ninety percent of all acute bronchitis cases are known to be of viral origin while the remaining ten percent are of bacterial origin (Albert, 2010; Kinkade and Long, 2016; Smith *et al*., 2017, Singh *et al*., 2019). About 6% of children worldwide have at least one episode per year of acute bronchitis (Wenzel and Fowler, 2006). Every year an episode of acute bronchitis is reported in approximately 5% of the adult population worldwide (Braman, 2006; Singh *et al*., 2019). This disease tends to affect women more than men (Wenzel and Fowler, 2006; Smith *et al.*, 2017). Factors such as overcrowding, smoking, living in a polluted place, and pre-existing respiratory diseases such as asthma are risk factors for acute bronchitis (Singh *et al*., 2019). Acute bronchitis can also be triggered by allergens such as pollen and perfumes (Singh *et al*., 2019).

A higher incidence of acute bronchitis is observed in the winter than in the other seasons (Wenzel and Fowler, 2006; Albert, 2010; Kinkade and Long, 2016; Smith *et al*., 2017; Singh *et al*., 2019). The incidence of acute bronchitis worldwide is known to range from 33 to 45 cases per 1000 annually, with an average number of 44 cases per 1000 annually (Smith *et al*., 2017). Patients that seek medical care for acute bronchitis account for more than ten million primary healthcare visits annually and this leads to ten ambulatory visits per 1000 people per year (Braman, 2006). Patients with acute bronchitis usually miss two to three days of work per episode in the United States of America (Smith *et al*., 2017).

In South Africa, acute bronchitis is a common reason for primary care visits and antibiotics are often given to treat this self-limiting condition, which is mostly of viral origin (Ncube *et al.*, 2017). More than 50% of patients having acute bronchitis in South Africa are prescribed an antibiotic, even though both national and international guidelines do not recommend the use of antibiotics (Ncube *et al*., 2017). The reasons for irrational medicine use when treating acute bronchitis in South Africa include patient demands and concerns about patient-doctor relationships (Ncube *et al.*, 2017).

1.3 Definition of acute bronchitis

Acute bronchitis, also known as viral bronchitis, is defined as an infection of the airways, mostly of viral origin, accompanied by a cough, sputum production, and periodically a burning retrosternal chest pain (National Department of Health, 2018). When acute bronchitis occurs in healthy individuals, it is referred to as, "uncomplicated acute bronchitis" (Braman, 2006). However, when acute bronchitis occurs in individuals who have pre-existing chronic diseases such as Chronic Obstructive Pulmonary Disease (COPD) and are at high risk for complications, it is referred to as, "complicated acute bronchitis" (Braman, 2006). The initial clinical feature is a non-productive cough, which is later followed by a productive cough with yellow or greenish sputum (National Department of Health, 2018).

Acute bronchitis is characterized by inflammation of the bronchi or large airways accompanied by a cough which may last for about three weeks (Braman, 2006; Tackett and Atkins, 2012). Acute bronchitis is a self-limiting illness, and it occurs in the absence of pneumonia (Braman, 2006; Tackett and Atkins, 2012). A cough is the main symptom for which patients with acute bronchitis seek medical care (Braman, 2006). In most patients with acute bronchitis, the cough usually lasts for ten to twenty days, with the average duration of cough being 18 days (Wenzel and Fowler, 2006). Since acute bronchitis is considered a self-limiting illness, other diagnoses should be considered if the cough persists for greater than three weeks (Braman, 2006).

1.4 Aetiology of acute bronchitis

Viral infections account for most cases of acute bronchitis, i.e., ninety percent, with bacterial infections accounting for the remaining ten percent and being more prevalent in patients with pre-existing chronic conditions (Wenzel and Fowler, 2006; Tackett and Atkins, 2012). Factors that determine the type of microorganism to be identified as a cause of acute bronchitis are the season of the year, the presence or absence of an epidemic, and the vaccination status of the patient (Wenzel and Fowler, 2006).

Viruses that are mostly identified in patients with acute bronchitis include parainfluenza, respiratory syncytial virus, influenza A and B (Braman, 2006; Tackett and Atkins, 2012). The viruses which are identified less commonly in patients with acute bronchitis are adenovirus, coronavirus, and rhinovirus (Tackett and Atkins, 2012). The most common bacterial causes of acute bronchitis are *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Bordetella pertussis* (Albert, 2010; Porter and Kaplan; 2011; Kinkade and Long, 2016). *Bordetella pertussis* is the most common cause of acute bronchitis, and it accounts for about nine percent of cases (Braman, 2006). *Mycoplasma pneumoniae* and *Chlamydia pneumonia* are rare causes of acute bronchitis and they both account for less than one percent of cases (Braman, 2006).

1.5 Pathophysiology of acute bronchitis

Acute bronchitis causes inflammation of the epithelium of the bronchi (Wenzel and Fowler, 2006; Singh *et al*., 2019). The inflammation of the bronchial wall causes epithelial cell desquamation, denunciation of the basement membrane, and mucosal thickening (Wenzel and Fowler, 2006; Singh *et al.,* 2019). Consequently, less air will flow through the bronchial tubes thus generating shortness of breath and chest tightness (Wenzel and Fowler, 2006; Singh *et al.*, 2019). The predominant symptom of acute bronchitis is a cough which may last for three weeks (Ward *et al.*, 2005; Porter and Kaplan, 2011; National Department of Health, 2018). The cough may occur with sputum production (National Department of Health, 2018). The other signs and symptoms of acute bronchitis include chills, chest discomfort, and shortness of breath (Wark, 2015). Additionally, burning retrosternal chest pain may also occur in some patients (National Department of Health,

2018). Tachycardia may occur indicating dehydration as well as fever secondary to the viral infection (Ward *et al.*, 2005; Singh *et al.,* 2019).

1.6 Diagnosis of acute bronchitis

The diagnosis of acute bronchitis is mainly clinical, and it should be differentiated from other conditions which present with similar symptoms (Table 1.1). The colour of the sputum does not indicate the aetiology of acute bronchitis hence it should not be used as a diagnostic measure in practice (Braman, 2006; Tackett and Atkins, 2012). The cough for acute bronchitis usually lasts for about 3 weeks hence a different diagnosis should be considered for a cough lasting greater than 3 weeks (Wenzel and Fowler, 2006; Tackett and Atkins, 2012). The patient should be assessed thoroughly by doing a physical examination, history taking and a smoking evaluation in order, to exclude other causes of the cough (Wenzel and Fowler, 2006; Tackett and Atkins, 2012).

Many respiratory diseases are often misdiagnosed as acute bronchitis mainly because of the similarity in some of the symptoms (Albert, 2010; Kinkade and Long, 2016; Singh *et al*., 2019). These respiratory diseases are referred to as differential diagnoses of acute bronchitis, and examples include acute asthma, Gastroesophageal Reflux Disease (GERD) and sinusitis (Albert, 2010; Kinkade and Long, 2016; Singh *et al*., 2019). For example, acute asthma is misdiagnosed as acute bronchitis in about one-third of patients who present with acute cough (Singh *et al*., 2019). The duration of cough is mainly used to distinguish between acute bronchitis and its differential diagnoses (Albert, 2010; Kinkade and Long, 2016). It is very important to ensure that no misdiagnoses occur when treating acute bronchitis in order, to prevent irrational medicine use and adverse effects (Albert, 2010).

Table 1.1: Differential diagnoses of acute bronchitis

Differential diagnosis	**Acute/ Chronic**	**Signs and symptoms**	**References**
Allergic rhinitis	Acute	Allergic rhinitis can present with	(Albert, 2010; Greiner *et al*., 2011)

		sneezing, a runny nose, red watery and itchy eyes, and this may not be present with acute bronchitis. The duration of cough for allergic rhinitis is shorter than that of acute bronchitis.	
Asthma	Usually chronic, except when it is an acute exacerbation of asthma	Asthma usually presents with wheezing and reversible airway obstruction while acute bronchitis does not present with both symptoms. The duration of cough for asthma is greater than that of acute bronchitis.	(Albert, 2010; Kinkade and Long, 2016)
Chronic Obstructive Pulmonary Disease (COPD)	Usually Chronic, except when there is an acute exacerbation	COPD presents with a chronic cough and airway obstruction while acute bronchitis has no airway obstruction and a shorter duration of	(Albert, 2010; Kinkade and Long, 2016)

		cough which is usually three weeks.	
Common cold	Acute	While the cough for the common cold customarily lasts for about seven to ten days, that of acute bronchitis usually lasts for three weeks.	(Little *et al.*, 2005; Kinkade and Long, 2016)
Gastroesophageal Reflux Disease (GERD)	Chronic	The duration of cough is used to differentiate between GERD and acute bronchitis. GERD is usually associated with a chronic cough that lasts longer than that of acute bronchitis.	(Albert, 2010; Kinkade and Long, 2016; Richter and Rubenstein, 2018)
Pneumonia	It can either be acute or chronic based on the duration of symptoms	Pneumonia can be excluded in acute bronchitis patients without specific clinical manifestations for pneumonia such as	(Metlay *et al.*, 1997; Braman, 2006; Wenzel and Fowler, 2006; Singh *et al*., 2019).

		tachycardia, fever, and tachypnea. Four prospective studies revealed that a chest X-ray is only recommended when the oral body temperature is > 38 degrees Celsius, the heart rate is >100 beats per minute, respiratory rate is > 24 breaths per minute, and when focal consolidation is observed because pneumonia is highly likely in the presence of these findings.	
Sinusitis	It can either be acute or chronic based on the duration of symptoms	The acute form of sinusitis can have a cough lasting for about 4 weeks while chronic sinusitis can last for 12 weeks or more. Sinusitis can present with facial	(Albert, 2010; Head *et al*., 2016)

		pain, a plugged nose, and thick nasal mucus while this may not be present with acute bronchitis.	

Numerous studies have shown that testing for C-reactive protein levels upon diagnosis helps to distinguish between pneumonia and acute bronchitis since pneumonia gives much higher levels of this biomarker compared to acute bronchitis (Albert, 2010; Held *et al.,* 2012; Kinkade and Long, 2016). C-reactive protein (CRP) is a normal plasma protein, whose circulating levels rise with an increase in inflammation and is measured in clinical practice to indicate diseases (Pepys and Baltz, 1983)

According to some researchers, it is still debatable whether the testing of procalcitonin levels is a good diagnostic measure for acute bronchitis (van Vugt *et al.,* 2013 and Schuetz *et al.,* 2018). Procalcitonin is a peptide precursor of the hormone calcitonin and the levels of procalcitonin rise with an increase in inflammation, especially that of bacterial origin (Dandona *et al*., 1994). Another study concluded that it is unnecessary to use procalcitonin to diagnose acute bronchitis which is mostly of viral origin because procalcitonin levels are frequently correlated with bacterial infections (Van Vugt *et al.,* 2013). However, another study strongly supported the testing of procalcitonin when diagnosing acute bronchitis (Schuetz *et al.*, 2018).

1.7 Treatment for Acute bronchitis

There are many evidence-based clinical, practice guidelines that are used in the treatment of acute bronchitis both nationally and internationally (Braman, 2006; Albert, 2010; Woodhead *et al*., 2011; Singh *et al.,* 2019). Many supportive and curative therapies are used to manage viral bronchitis such as analgesics, antipyretics, antivirals, antitussives, expectorants, and complementary medicines (Albert, 2010; Porter and Kaplan, 2011; Little *et al*. 2013; Kinkade and Long, 2016; Smith *et al*., 2017; Singh *et al*., 2019).

1.7.1 Access to healthcare in South Africa

Since the establishment of the country's new democratic administration in 1994, and the subsequent implementation of the National Drug Policy (NDP), announced in 1996, the healthcare landscape in South Africa has changed dramatically (Pillay and Suleman, 2017). Since then, the government has been engaging in a healthcare reform to ensure fair access to healthcare and medicines for all citizens, particularly those historically disadvantaged by the apartheid system's racially fragmented and under-resourced healthcare systems (Pillay and Suleman, 2017). In South Africa, the healthcare system is still divided into two tiers, with public and private sectors (Pillay and Suleman, 2017). There are three stages of care in the public sector, i.e., primary care, secondary care, and tertiary care (Pillay and Suleman, 2017).

The establishment of a Ministerial appointed National Essential Medicines List Committee (NEMLC) was one of the primary goals of the NDP for South Africa's essential drugs programme (EDP), which was responsible for the preparation of an essential medicines list (Pillay and Suleman, 2017). The Standard Treatment Guidelines and Essential Medicines List (STGs/EML) that resulted were first published in 1996 at the primary healthcare level, followed by secondary and tertiary hospital levels in later years, with different editions for adults and children (Pillay and Suleman, 2021). The STGs/EML were supposed to redress the discrepancies in access to healthcare and pharmaceuticals left over from the apartheid administration by assuring a standard quality of care for all citizens seeking treatment in a public sector facility (Pillay and Suleman, 2021). In South Africa, the process of selecting medicines in accordance with STGs is not easily accessible to the public (Pillay and Suleman, 2017). Little is known about the NEMLC's drug selection processes or how they have evolved over time (Pillay and Suleman, 2017). As a result, more studies should be done on this so that problems are identified, and solutions are sought (Pillay and Suleman, 2017).

The introduction of an EML was supposed to cut drug costs and increase rational use by assuring that only a small number of essential medicines would be classified and procured (Pillay and Suleman, 2017). The NDP implemented generic substitution in 2003 to further

reduce spending (Gray *et al*., 2016). The goal of this policy was to bring generic prescribing to both the private and public sectors (Gray *et al.*, 2016). The NDP was dedicated to the use of interchangeable multisource pharmaceutical products (IMPP) or generics, referred to by the international non-proprietary name (INN) or generic name (Gray *et al.*, 2016). Medicines on the National Essential Medicines List are mostly generic because substitution is not allowed in public sector facilities, since only those drugs bought through tender are available. (Gray *et al.*, 2016).

The tender process, which has been in place since 1982, is used to buy medicines in the public sector (Wouters *et al*., 2019). In essence, the procedure is the bulk purchase of drugs at a predetermined price for a set length of time after a competitive bidding process (Wouters *et al.*, 2019). All interested parties are welcome to submit bids if they have marketing authorization from the national medicines' authority (Wouters *et al*., 2019). The government's tender quantities are based on previous year's usage patterns and epidemiological projections (Wouters *et al.*, 2019). The figures are not enshrined in law, and the government may propose lower or higher sums (Wouters *et al*., 2019). The bidding process is intended to increase competition among generic medicine manufacturers and lower drug prices (Wouters *et al*., 2019).

The private sector uses less generics than the public sector because they can afford more originator medicines (Gray *et al.*, 2016). Healthcare services in the private sector are primarily funded by medical aid schemes, with a small portion funded by out-of-pocket payments (Modisakeng *et al*., 2020). The high expense of medical aid schemes has prevented the mass of the populace from accessing healthcare services in the private sector (Modisakeng *et al*., 2020). Generic substitution is very important because it improves access to health care, and it will enable the sustainability of the UHC system in South Africa once it has been fully implemented (Gray *et al.*, 2016).

The World Health Organization's Universal Health Coverage (UHC) principle guarantees equal access to medicines and healthcare (Pillay and Suleman, 2021). Universal health coverage means that everyone can get the health care they need, when and when they need it, without having to pay a lot of money. It covers the entire spectrum of basic health services, from prevention to treatment, rehabilitation, and palliative care (Pillay and

Suleman, 2021). South Africa is currently an upper-middle-income country that is working to achieve universal health coverage (UHC) through the National Health Insurance (NHI) policy funding effort (Pillay and Suleman, 2021).

The NHI is intended to close the gap in healthcare disparity that still exists in South Africa as a result, of the country's two-tiered public and private healthcare systems (Pillay and Suleman, 2021). Large distances and high travel costs, especially in rural regions; high out-of-pocket (OOP) payments for care, long lines, and disempowered people are all impediments to access (Harris *et al*., 2011). These access constraints, which are caused by unequal social power relationships, are like those seen in other low- and middle-income countries (LMICs) (Harris *et al*., 2011). The shortcomings of current healthcare and essential medicines policies must be investigated in order, to develop recommendations for ensuring UHC access to medicines (Pillay and Suleman, 2021). This is especially significant given that the STGs/EML is to be used efficiently in the NHI finance mechanism (Pillay and Suleman, 2021).

Primary health care is defined as crucial health care built upon evidence-informed and socially tolerable methods which are made generically accessible to communities at an affordable cost to promote self-sufficiency (World Health Organization, 1978). Primary care is a very important component of any health system because it is the first level of contact for patients as well as the community (World Health Organization, 1978).

The World Health Organization (1978) declared that a primary healthcare facility should provide immunization against infectious diseases and appropriate medicines to treat infectious diseases such as Acute bronchitis. For Acute bronchitis, which is a communicable disease, primary healthcare settings offer services which are for health promotion and disease prevention (National Department of Health, 2016).

Vaccines are used most often as a preventative measure for acute bronchitis (Singh *et al.*, 2019). Influenza vaccines, pertussis vaccines, and pneumococcal conjugate vaccines are administered regularly during the winter months to prevent acute bronchitis (Singh *et al.*, 2019). Moreover, vaccines are highly recommended for special population groups such as babies younger than two years but older than six months, pregnant women, adults aged 65

or more, and residents of nursing homes or long-term care facilities (Singh *et al.*, 2019). Recent evidence reports that influenza vaccines are the most common vaccines given to South Africans to prevent acute respiratory tract infections such as acute bronchitis (National Institute of Communicable Diseases, 2020).

1.7.2 Anatomical Therapeutic Chemical (ATC) Classification System

Medicines used to treat acute bronchitis are classified using the ATC/DDD system (WHO, 2020). The abbreviation ATC stands for Anatomical Therapeutic Chemical, while the abbreviation DDD stands for Defined Daily Dose (WHO,2020). The ATC/DDD system as a global standard made by the WHO where active ingredients in a medicine, are classified by the organ or body system on which they have an impact (WHO, 2020; Hollingworth and Kairuz, 2021). The ATC/DDD system is intended to be used as a tool for drug utilization monitoring and research in order, to improve drug quality (WHO, 2020; Hollingworth and Kairuz, 2021). One of the most significant goals of drug use is to track both rational and irrational drug use as a means of enhancing the quality of drug use (WHO, 2020). One of the key goals of the ATC/DDD system is to keep ATC codes and DDDs stable over time so that patterns in drug usage may be tracked without the difficulty of periodic system modifications (WHO, 2020).

The active ingredients are categorized in the ATC classification system in a five-level hierarchy (WHO, 2020; Hollingworth and Kairuz, 2021). The first levels of the system are divided into fourteen anatomical/pharmacological groupings (WHO, 2020; Hollingworth and Kairuz, 2021). Each ATC primary category is subdivided into two levels, with the second level being either pharmacological or therapeutic (WHO, 2020; Hollingworth and Kairuz, 2021). The 3rd and 4th levels are chemical, pharmacological, or therapeutic subgroups, and the 5th level is the chemical substance (WHO, 2020; Hollingworth and Kairuz, 2021).

Most medicines used to treat acute bronchitis fall under the therapeutic subgroup called referred to as, cough and cold preparations (WHO, 2020). The pharmacological subgroups for treating acute bronchitis include expectorants, cough suppressants, combination

medicines and other cold preparations (WHO, 2020). The anatomical main group of medicines commonly used to treat acute bronchitis is R, which stands for Respiratory System (WHO, 2020). Using acetylcysteine as an example, it is classified as respiratory which is the body system, followed by the 2nd level therapeutic subgroup, i.e., Cough and cold preparations, followed by the 3rd level pharmacological subgroup, i.e., Expectorants excluding cough suppressants, followed by the 4th level chemical subgroup, i.e., Mucolytics and finally the 5th level chemical descriptor, i.e., acetylcysteine with the ATC code of R05CB01 (WHO, 2020).

The Defined Daily Dose (DDD) is the daily average maintenance dose for a medication used in adults for its primary indication (WHO, 2020). The DDD was created to address challenges with dosage forms and is also a handy tool to track changes in use over time, particularly when the mix of formulations varies or when pack sizes change, as is common in many healthcare settings (Hollingworth and Kairuz, 2021). The DDD is a measuring unit that does not always correspond to the recommended or prescribed daily dose (PDD) (WHO, 2020; Hollingworth and Kairuz, 2021). The PDD is defined as the average dose prescribed based on a representative sample of prescriptions (Hollingworth and Kairuz, 2021).

Individual therapeutic doses, and patient groups will frequently deviate from the DDD due to individual variables such as age, weight, ethnic variances, disease type or severity, and pharmacokinetic considerations (WHO, 2020). Only one DDD is given for each ATC code, and route of administration e.g., oral (WHO, 2020). Topical products, sera, vaccinations, antineoplastic medicines, allergen extracts, general or local anaesthetics, and contrast media do not have DDDs (WHO, 2020). The DDDs assigned to combination medicines are based on the principle of counting the combination as a single daily dosage, regardless of the number of active ingredients in the combination (WHO, 2020). If a patient's treatment plan includes two single-ingredient products, for instance, the consumption will be calculated by counting the DDDs for each single-ingredient product separately (WHO, 2020). Using acetylcysteine as an example, the DDD is 1.6g for the inhalation route of administration and 0.5g for the oral route of administration (WHO, 2020).

1.7.3 Evidence-based clinical practice guidelines

Ncube *et al.* (2017) reported that South African and international evidence-based clinical practice guidelines for acute bronchitis correspond. The findings of Braman (2006), Albert (2010), Woodhead *et al.* (2011) and Singh *et al.* (2019) all reveal that adherence to evidence-based clinical practice guidelines in the treatment of acute bronchitis optimizes patient outcomes. Firstly, the National Department of Health (2018) recommends that in the absence of an underlying chronic obstructive pulmonary disease, antibiotics must not be given for acute bronchitis. Comparably, the National Institute for Health and Care Excellence (2016) recommends that no immediate or delayed antibiotic regimen should be prescribed for a patient having acute bronchitis unless the patient has an underlying chronic ailment. According to Spurling *et al*. (2017), a delayed antibiotic regimen means the delay made in the filling of an antibiotic prescription by at least 48 hours.

Moreover, the joint task force of the European Respiratory Society and the European Society for Clinical Microbiology and Infectious Diseases recommends that an antibiotic can be prescribed for acute bronchitis if the patient has an underlying chronic condition, with the first-line treatment being amoxicillin or doxycycline (Woodhead *et al.*, 2011). Analogously, the American Academy of Pediatrics (2015) recommends that antibiotics must not be given for self-limiting respiratory tract infections such as acute bronchitis.

Furthermore, the American College of Chest Physicians recommends that antibiotics must not be given for acute bronchitis unless a bacterial infection exists (Braman, 2006; Albert, 2010; Woodhead *et al.*, 2011; Singh *et al.*, 2019). The Infectious Diseases Society of America recommends that antibiotics must not be prescribed for acute respiratory tract infections because these are mostly self-limiting and of viral origin (Kinkade and Long, 2016). More recent evidence states that a macrolide such as azithromycin is the antibiotic of choice for acute bronchitis caused by *Bordetella pertussis* (Kinkade and Long, 2016; Singh *et al.*, 2019). Additionally, a macrolide can also be given to a patient in cases of penicillin allergy (Woodhead *et al.*, 2011).

Table 1.2: Treatment guidelines for acute bronchitis

Type of Evidence-based clinical practice guideline	Recommendation/s	References
The American Academy of Pediatrics	Antibiotics must not be used to treat self-limiting respiratory tract infections such as acute bronchitis.	(American Academy of Pediatrics, 2015).
American College of Chest Physicians	Antibiotics must not be given for acute bronchitis unless a *Bordetella pertussis* infection exists.	(Braman, 2006; Albert, 2010; Woodhead *et al.*, 2011; Singh *et al.*, 2019)
Infectious Diseases Society of America	Antibiotics should not be given for acute respiratory tract infections.	(Kinkade and Long, 2016)
The Joint task force of the European Respiratory Society and the European Society for Clinical Microbiology and Infectious Diseases	An antibiotic may be required to treat a secondary bacterial infection, if so, amoxicillin or doxycycline should be the first choice. A macrolide or tetracycline is a good alternative if there is a penicillin allergy.	(Woodhead *et al.*, 2011)
NICE guidelines	Unless a patient is at	(National Institute of Healthcare

	high risk, no antibiotic should be given to the patient. According to the NICE guidelines, a patient is at high risk if he or she is systemically very unwell, has symptoms suggestive of serious illness or complications, is at risk of complications because of a pre-existing condition, is a premature baby, or is greater than 65 years old with an acute cough, along with two or more of the following criteria (or greater than 80 years old with acute cough and one or more of the following criteria): (i) hospitalization in the previous year; (ii) having type 1 or type 2 diabetes; (iii) history of congestive heart failure; and (iv) current taking oral glucocorticoids. For such high-risk	Excellence, 2016)

	patients, antibiotics can be recommended.	
Standard Treatment Guidelines of South Africa/Essential Medicines List for Primary Health Care	Antibiotics are not indicated in acute bronchitis in the absence of an underlying Chronic Obstructive Pulmonary Disease. It is very important to exclude pre-existing bronchiectasis or an acute exacerbation of chronic bronchitis in adults.	(National Department of Health, 2018)

1.7.4 Medicines used to treat acute bronchitis

Many therapies such as analgesics, antipyretics, antivirals, antitussives, expectorants, and complementary medicines are used by patients having acute bronchitis to manage their symptoms (Albert, 2010; Porter and Kaplan, 2011; Little *et al.* 2013; Kinkade and Long, 2016; Smith *et al.*, 2017; Singh *et al.*, 2019). Centrally acting agents such as codeine, hydrocodone and dextromethorphan are often used to treat a cough associated with acute bronchitis in clinical practice (Smith *et al.*, 2017; Woodhead *et al*., 2011).

Historically, there has been a great deal of confusion in the literature regarding the use of hydrocodone, dextromethorphan, and codeine for acute bronchitis (Braman, 2006; Albert, 2010). These centrally acting agents or antitussives are not recommended for treating a cough caused by acute bronchitis because of their minimal therapeutic benefits (Smith *et al*., 2017; Woodhead *et al*., 2011). There is a lack of sufficient evidence to support their use for a cough associated with acute bronchitis (Singh *et al*., 2019). The American College of Chest Physicians strongly prohibits the routine use of codeine to manage a cough caused by acute bronchitis because of its minimal therapeutic benefits and its potential for addiction (Woodhead *et al*., 2011).

Dextromethorphan can be used instead of codeine because it does not potentiate addiction, it has more therapeutic benefits, and has fewer adverse effects (Martinak *et al*., 2017). However, if dextromethorphan is used in very large doses, it can cause some form of psychosis characterized by delusions, hallucinations, and paranoia (Martinak *et al*., 2017). Little *et al*. (2013) reported that paracetamol, steam inhalation, and ibuprofen moderately improve the symptoms of acute bronchitis, with paracetamol being more effective than ibuprofen. In contrast, Kinkade and Long (2016) reported that ibuprofen did not show any benefit for acute bronchitis in one randomized clinical trial.

Expectorants such as guaifenesin are also used regularly to treat the cough and reduce mucous viscosity in patients with acute bronchitis (Kinkade and Long, 2016; Smith *et al*., 2017; Singh *et al*., 2019). Guaifenesin is highly recommended to ease a cough associated with acute bronchitis because it was found to reduce cough frequency and intensity by 75%, while a placebo had a reduction of 31% in one clinical trial (Kinkade and Long, 2016). Guaifenesin is known to produce antitussive effects which are responsible for treating the cough associated with acute bronchitis (Kinkade and Long, 2016). Guaifenesin also acts by increasing secretions in the respiratory tract, thus increasing volumes of respiratory fluids, and decreasing mucous viscosity (Kinkade and Long, 2016).

Antihistamines such as cetirizine, are frequently utilized as first-line treatment for alleviating symptoms of acute bronchitis (Smith *et al*., 2017). Antihistamines should not be routinely used in the management of acute bronchitis because they give scarcely any therapeutic benefits and increase adverse effects (Kinkade and Long, 2016; Smith *et al.*, 2017). In addition, two clinical trials performed on antihistamines alone showed no benefit at all when compared to a placebo (Kinkade and Long, 2016). However, antihistamines show moderate benefits when used in combination with nasal decongestants to treat symptoms of acute bronchitis (Kinkade and Long, 2016).

Nasal decongestants such as pseudoephedrine should not be routinely used in the management of acute bronchitis because they give hardly any therapeutic benefits and increase adverse effects (Kinkade and Long, 2016; Smith *et al.*, 2017; Singh *et al.*, 2019). However, nasal decongestants show moderate benefits when used in combination with antihistamines (Kinkade and Long, 2016; Smith *et al.*, 2017; Singh *et al.*, 2019). Most nasal decongestants such as oxymetazoline are known to cause rebound congestion if they are used excessively (South African Medical Association, 2020). It is recommended to use nasal decongestants in combination with other medicines as this does not potentiate rebound congestion (South African Medical Association, 2020).

β_2 agonists are recommended for patients with a cough affiliated with wheezing and airflow obstruction only (Becker *et al.,* 2015; Kinkade and Long, 2016; Singh *et al.*, 2019). In one clinical trial done for albuterol/salbutamol in adults with acute bronchitis, therapeutic benefits were observed in patients with wheezing and airflow obstruction only (Becker *et al.*, 2015; Kinkade and Long, 2016). Additionally, albuterol/salbutamol did not show any benefit in reducing cough in the absence of wheezing and airflow obstruction, for two clinical trials that were performed on children (Becker *et al.,* 2015; Kinkade and Long, 2016). β_2 agonists are also not recommended for acute bronchitis because of their high potential to cause tremors and nervousness (Becker *et al.,* 2015; Kinkade and Long, 2016). β_2 agonists are recommended for acute asthma and not for acute bronchitis (National Department of Health, 2018; South African Medical Association, 2020).

Corticosteroids are not recommended for acute bronchitis since there is insufficient evidence to support their therapeutic benefits (Albert, 2010; Becker *et al.*, 2015; Singh *et al.,* 2019). They are also not recommended because they have many adverse effects such as hyperglycaemia, increase in blood pressure, and fluid retention (Becker *et al.,* 2015). Corticosteroids such as prednisone should not be used in patients with acute bronchitis, having no pre-existing chronic condition such as asthma (Becker *et al.*, 2015; Singh *et al.,* 2019). One study recommends the use of inhalational corticosteroids such as fluticasone for acute bronchitis (Albert, 2010). High dose, episodic inhaled corticosteroids have shown therapeutic benefits in relieving symptoms of acute bronchitis, while no benefits have been observed with low dose, preventative therapy (Albert, 2010).

Complementary medicines are mostly used in the management of acute bronchitis particularly one called South African *geranium* (Timmer *et al.*, 2013). The South African *geranium* is usually referred to as the *folk remedy rabassam, Pelargonium sidoides, or kalwerbossie* and is known to produce moderate effectiveness in the management of acute bronchitis (Timmer *et al.*, 2013). In most randomized clinical trials, which were performed for *kalwerbossie*, a modest reduction of symptom severity has been observed in patients presenting with acute bronchitis (Chuchalin *et al.*, 2005). In one randomized clinical trial for acute bronchitis, patients taking *kalwerbossie* returned to work two days earlier than patients taking a placebo (Matthys *et al.*, 2003).

Yale and Liu (2004) disclosed that *Echinacea* can be used to alleviate symptoms of acute bronchitis. Multiple clinical trials have shown that *Echinacea purpurea* produces modest benefits in alleviating symptoms of acute bronchitis and these benefits are better than those for a placebo (Yale and Liu, 2004). Additionally, Chinese traditional herbs such as *huoke* granules and *Xiaoer Shangfeng Zhike tangjiang* syrup have been used for so many years for acute bronchitis, but there is little evidence to support their therapeutic benefits (Jiang *et al.*, 2012). In one randomized clinical trial, *Xiaoer Xiaoji Zhike Koufuye* oral decoction was found to be more effective in minimizing symptoms of acute bronchitis than cefotaxime and N-acetylcysteine (Wu *et al.*, 2008).

Furthermore, *Yuxingcao* atomization aerosol was found to be more effective than gentamycin in attenuating a cough, fever, and rales associated with acute bronchitis (Wu *et al.*, 2008). Analogously, *Shiwei Longdanhua Keli* oral decoction and *Tanreqing* injection were observed to diminish the frequency and intensity of a cough, rales, and fever brought about by acute bronchitis to a greater extent compared to antibiotics such as levofloxacin (Wu *et al.*, 2008). Notwithstanding the safety concerns and lack of information regarding the pharmacovigilance aspects of traditional Chinese medicines, these medicines continue to be used regularly to attenuate symptoms of acute bronchitis (Jiang *et al.*, 2012).

In the opinion of Oduwole *et al.* (2014), honey is better than no treatment in alleviating a cough associated with acute bronchitis and it improves the quality of sleep. In a certain clinical trial done for acute bronchitis, dark honey was found to be more effective than dextromethorphan and diphenhydramine in alleviating symptoms in children (Paul *et al.*, 2007). Singh *et al.* (2019) stated that the combination of honey, ginger, and hot tea is very effective in attenuating the cough affiliated with acute bronchitis, although no clinical trials have been done on these therapies. Moreover, Oduwole *et al.* (2014) reported that it is better to give honey to acute bronchitis patients than antitussives for alleviating a cough because antitussives have many adverse effects. Vitamin C is highly recommended for acute bronchitis because this vitamin improved symptoms significantly in a study involving 230 patients (Evans *et al.*, 2002).

Table 1.3: Recommendations for complementary medicines

Name of Complementary medicine	**History of Clinical trials**	**Recommendations**	**References**
Chinese traditional medicines	Several randomized clinical trials on patients with acute bronchitis showed that these medicines are excellent at reducing the severity of symptoms of acute bronchitis.	These medicines are routinely used in clinical practice although there is a lack of information regarding their pharmacovigilance aspects.	(Wu *et al.*, 2008; Jiang *et al.*, 2012)
Echinacea	Multiple randomized clinical trials on acute bronchitis patients have shown that *Echinacea purpurea*	It is highly recommended to take this medicine to alleviate symptoms of acute bronchitis.	(Yale and Liu, 2004)

	produces modest benefits in alleviating symptoms of acute bronchitis and these benefits are better than those for a placebo		
Ginger	The combination of honey, ginger, and hot tea is known to be effective in attenuating the cough affiliated with acute bronchitis although no clinical trials have been done on ginger.	It is often recommended although there is insufficient evidence to support its use.	(Singh *et al*., 2019)
Honey	In a certain randomized clinical trial done for acute bronchitis patients, dark honey was found to be more effective than dextromethorphan and diphenhydramine in alleviating symptoms in children. Honey is highly effective when used in combination with ginger and tea.	It is often recommended in clinical practice for acute bronchitis.	(Paul *et al.,* 2007; Oduwole *et al*., 2014; Singh *et al.,* 2019)

South African *geranium*	In multiple randomized clinical trials for patients with acute bronchitis, which were done for *kalwerbossie*, a modest reduction of symptom severity has been observed in patients presenting with acute bronchitis.	It is often recommended to take this medicine since it reduces the severity of symptoms.	(Matthys *et al.*, 2003; Chuchalin *et al.*, 2005; Timmer *et al.*, 2013)
Vitamin C	In a randomized clinical trial involving 230 patients having acute bronchitis, vitamin C exhibited a significant improvement in symptom severity after administration thus vitamin C is highly recommended for acute bronchitis.	It is highly recommended in clinical practice for acute bronchitis.	(Evans *et al.*, 2002)

Singh *et al.* (2019) concluded that oseltamivir and zanamivir are the antivirals of choice in treating acute bronchitis caused by an *influenza* virus. Oseltamivir and zanamivir are both recommended for the prophylaxis and treatment of influenza infections (Centre for Disease Control and Prevention, 2020; National Institute of Communicable Diseases, 2020). Antiviral treatment using oseltamivir or zanamivir can be given immediately before laboratory confirmation of *influenza* (The Centre of Disease Control and Prevention, 2020). Amantadine and rimantadine are two antivirals that are not recommended for *influenza* infections because of resistance (National Institute of Communicable Diseases, 2020).

Oral oseltamivir and inhaled zanamivir are commonly given in the winter season to treat influenza infections in South Africa (National Institute of Communicable Diseases, 2020). These two antivirals are related chemically, and they act by inhibiting viral neuraminidases (National Institute of Communicable Diseases, 2020). The National Institute of Communicable Diseases (2020) established the dosing regimens for influenza infections according to different age groups. Inhaled zanamivir is strongly recommended to be used only in patients aged 7 years and above, and where there is an oseltamivir-resistant influenza infection (National Institute of Communicable Diseases, 2020). Since zanamivir contains lactose powder for inhalation, it must not be used with a nebulizer as it may negatively affect the breathing capacity of the patient (National Institute of Communicable Diseases, 2020).

1.7.5 Antibiotic use for acute bronchitis

Several studies suggest that antibiotics are regularly used for acute bronchitis although this is against evidence-based clinical practice guidelines (Goossens *et al.*, 2005; Albert, 2010; Gulliford, 2014; Shapiro, 2014; Kinkade and Long, 2016; Ncube *et al.*, 2017; Singh *et al.*, 2019; Engler *et al.*, 2020). Simpson *et al.* (2007) established factors that cause irrational antibiotic prescribing in primary care. These factors include patient demands and complaints, ignorance, prescribers' self-confidence, daily pressures from clinical practice, various health policies, and research discoveries (Simpson *et al.*, 2007). In the opinion of

Togoobaatar *et al.* (2010), the effects of inappropriate antibiotic use are antimicrobial resistance, increased treatment costs, wastage of resources, adverse effects, and eroded patient confidence.

Preceding studies indicate that the use of antibiotics in the management of acute bronchitis does not bring any therapeutic benefit (Albert, 2010; Kinkade and Long, 2016). A review of nine randomized clinical trials found that antibiotics produced insignificant benefits in symptom relief for acute bronchitis (Singh *et al.,* 2019). Many health care providers give antibiotics for acute bronchitis in patients presenting with green or yellow sputum (Butler *et al.,* 2011; Kinkade and Long, 2016). However, one study showed that the sputum colour does not determine if it is a bacterial infection (Butler *et al.,* 2011; Kinkade and Long, 2016).

A study was done previously in South Africa to evaluate antibiotic prescribing for acute respiratory tract infections (Katende-Kyenda *et al.,* 2007). The study was done in nine primary care facilities for influenza, acute sinusitis, and acute bronchitis (Katende-Kyenda *et al.,* 2007). Katende-Kyenda *et al.* (2007) revealed that male patients received fewer antibiotics at a rate of 38.31% compared to females who received antibiotics at a rate of 61.44%. In addition, it was observed that amoxicillin 250mg was routinely given for acute bronchitis (Katende-Kyenda *et al.,* 2007). Amoxicillin was given in 23 989 cases, of which 14 363 cases incorporated females while the other 9 626 cases incorporated males (Katende-Kyenda *et al.,* 2007). The overall rate of inappropriate antibiotic prescribing for acute bronchitis was found to be 38.17% (Katende-Kyenda *et al.,* 2007).

Another study was conducted in South Africa to evaluate antibiotic prescribing for acute respiratory tract infections including acute bronchitis (Ncube *et al.,* 2017). Health insurance schemes' claims were analyzed to assess antibiotic prescription patterns (Ncube *et al.,* 2017). There were 166 821 cases of acute bronchitis all over South Africa throughout the time of the study (Ncube *et al.,* 2017). There were 34% of cases from Gauteng Province, 5.0% from the Northern Cape, 17.2% from Western Cape province, and 15.6% from KwaZulu-Natal (Ncube *et al.,* 2017). Additionally, 10.4% cases were from Eastern Cape

province, 6.2% from Mpumalanga, 3.0% from Northwest, 2.1% from Limpopo, and 6.4% from Free State province (Ncube *et al.*, 2017). The overall rate of inappropriate antibiotic prescribing was 52.9%. Ncube *et al.* (2017) stated the classes of antibiotics prescribed and were cephalosporins, tetracyclines, fluoroquinolones, sulfonamides, macrolides, and penicillins.

1.8 Legality of prescriptions and medicine labels

1.8.1 Prescriptions

Regulation 33, of the Medicines and Related Substances Control Act 101 of 1965 as amended, provides the legal requirements on rational prescribing practices and what is required on a prescription (South African Pharmacy Council, 2017). According to the Medicines and Related Substances Control Act 101 of 1965 as amended, a prescription is defined as a set of written or verbal instructions given to an authorized dispenser by an authorized prescriber for the selection, preparation, and dispensing of a medicine for a patient (South African Pharmacy Council, 2017). The Medicines and Related Substances Act 101 of 1965, as amended, outlines the legal requirements for a prescription which indicate that medicines should only be prescribed if the benefits outweigh the risks to the patient (South African Pharmacy Council, 2017). Regulation 33 of the Medicines and Related Substances Act 101 of 1965, as amended, also shows the particulars which must appear on the prescription for a medicine (South African Pharmacy Council, 2017). Refer to Appendix C in order, to see an example of a prescription for acute bronchitis.

Some authors suggest that prescribers often do not comply with the legislation when writing prescriptions (Brits *et al.*, 2017). Very few studies have been done in South Africa to evaluate the compliance to legislation by prescribers when issuing prescriptions (Brits *et al*, 2017). In one study, the prescriptions did not have the duration and route of administration and in some prescriptions these two legal requirements were not observed on prescriptions sue to the illegible handwriting (Brits *et al*., 2017).

It is widely assumed that doctors' handwriting is illegible (Brits *et al*., 2017). The writer usually knows what is written, but when other parties are involved, they frequently have difficulty reading and interpreting the content (Brits *et al*., 2017). A 42-year-old American died when the pharmacist gave him Isordil® (Isosorbide dinitrate), which he mistook for Plendil® (Felodipine) due to the doctor's illegible handwriting, according to a report published in the British Medical Journal (Brits *et al*., 2017). Expert pharmacists found 2% of prescriptions difficult to read or illegible, compared to 21.6 percent of non-expert pharmacists, according to research conducted in Saudi Arabia (Albarrak *et al*., 2014). In a hospital environment, an Italian research project found unclear handwriting in 24 percent of prescriptions (Calligaris *et al*., 2009). Even when doctors were encouraged to write as neatly as possible, their handwriting was still more unintelligible than that of those in other professions, according to one research project (Brits *et al*., 2017).

In South Africa, there is very little information about doctors' handwriting on prescriptions (Brits *et al*., 2017). Every year, more than a million people are affected by preventable medication errors (Brits *et al*., 2017). Uncertain abbreviations, dosages, and poor handwriting on prescriptions all contribute to these errors (Brits *et al*., 2017). As a result, doctors have been urged to use digital prescriptions to avoid such mistakes (Nanji *et al*., 2011). However, some studies have found that electronic prescriptions do not reduce frequent prescription errors that occur when prescriptions are written by hand (Nanji *et al*., 2017). Despite the computer revolution, most of the prescriptions are still handwritten.

1.8.2 Medicine labels

The National Department of Health (2017) declared that a label made for any dispensed medicine must be per regulation 8 of the Medicines and Related Substances Act 101 of 1965, as amended. The contents of the label for a dispensed medicine must appear in clearly legible, indelible letters in English and at least one other official language in South Africa (National Department of Health, 2017). In addition, every label for a dispensed medicine is expected to comply fully with the relevant legislation (National Department of Health, 2017).

Labels of medication can also be given for medicines that have undergone pre-packing according to section 2.19 of the Good Pharmacy Practice (GPP) manual and the Medicines and Related Substances Act 101 of 1965, as amended (National Department of Health, 2017). Pre-packing means the repacking of medicines from bulk containers into smaller containers (National Department of Health, 2017). During pre-packing, care must be taken to ensure that there is no mix-up between packaging material, labels, and plastic bags (National Department of Health, 2017). Refer to Appendix D1 in order, to see an example of a label for a dispensed medicine and Appendix D2 in order, to see an example of a label for a dispensed medicine that has undergone pre-packing for acute bronchitis.

The labelling process includes providing information and instructions to ensure the patient's safe and effective usage of the medicines (Neoh *et al*., 2009). The label of a dispensed medicine is one of the most essential sources of information for patients (Neoh *et al*., 2009). The label should include accurate information regarding the medicine's name, how, when, and why it should be used (Neoh *et al*., 2009). This information should be given in a way that patients can understand and act on (Shrank *et al*., 2007). However, written material on medicine labels is sometimes inconsistent, incomplete, or difficult to comprehend for patients (Shrank *et al*., 2007).

Medication labelling issues have been mentioned as a possible cause of medication errors (Shrank *et al*., 2007). According to one American study, roughly 1.5 million medication errors occur in the United States each year owing to incorrect medicine labelling (Neoh *et al*., 2009). As a result, proper medication labelling is critical in ensuring that medicines are taken safely (Neoh *et al*., 2009). Furthermore, patients' inability to comprehend medicine labels has resulted in increased hospitalization rates (Neoh *et al*., 2009). Consequently, appropriate medicine labelling practices by health care professionals may help to prevent medication errors and possibly reduce patient hospitalization rates (Neoh *et al*., 2009). Very few studies have assessed the compliance to legislation for medicine labels (Neoh *et al*., 2009). In addition, there is insufficient data on the impact of current labelling practices by health professionals towards patients' safety (Neoh *et al*., 2009).

1.9 Dangers of irrational medicine use for acute bronchitis

1.9.1 Pharmacovigilance aspects

According to the World Health Organization (2002), pharmacovigilance is defined as the science and activities associated with the identification, evaluation, understanding as well as prevention of any adverse drug reaction or medicine-related problem. Several authors have reported that the irrational use of medicines for acute bronchitis can lead to serious adverse effects (Albert, 2010; Togoobaatar *et al.,* 2010; Garg *et al.*, 2014; Kinkade and Long, 2016). An adverse drug reaction is defined as a response to a medicine that is harmful, unintended, and occurs at any dose (National Department of Health, 2017).

Kinkade and Long (2016) reported that the irrational prescribing of antibiotics for acute bronchitis can cause many adverse effects worldwide. Additionally, Albert (2010) reported that a meta-analysis done on the use of antibiotics for acute bronchitis showed that patients only had adverse effects and no clinical improvement. β_2 agonists were found to cause intense tremors and nervousness in acute bronchitis patients, with limited therapeutic benefits (Kinkade and Long, 2016). Numerous Chinese herbal medicines are used recurrently for acute bronchitis worldwide, but no pharmacovigilance investigations have been done to assess their safety (Kinkade and Long, 2016).

Some adverse effects of medicines for acute bronchitis are caused by drug-drug interactions (Albert, 2010; Kinkade and Long. 2016). A drug-drug interaction (DDI) is an activity that one drug has on another, resulting in a quantitative or qualitative alteration in the effects of both (Ziehl *et al*., 2019). Clinicians frequently administer many medicines at the same time in order, to achieve a greater therapeutic effect, which raises the risk of adverse drug effects (ADEs) due to DDIs (Ziehl *et al*., 2019). In healthcare settings, ADEs caused by DDIs are a critical challenge (Ziehl *et al.*, 2019). The harmful effects of drug-drug interactions can be avoided by appropriately identifying important DDIs prior to therapy, considering pharmacological characteristics, delivery routes, and patient-specific

variables (Ziehl *et al*., 2019). For health professionals, there are a variety of databases that provide information about drugs and their potential pharmacological interactions (Ziehl *et al*., 2019). Medscape®, Micromedex®, and Lexicomp® are the most regularly utilized databases, all of which use an algorithm to determine the prevalence and clinical significance of DDIs (Ziehl *et al*., 2019).

Most adverse effects which are caused by drug-drug interactions when treating acute bronchitis are due to Oral Inhaled Medicines (OIMs) (Ajimura *et al*., 2018). Common OIMs given for acute bronchitis include β_2 agonists, antimuscarinics, corticosteroids, antibiotics, mucolytics, antivirals, and combination products (Ajimura *et al*., 2018). Pharmacodynamic and pharmacokinetic interactions are two types of drug-drug interactions commonly found among medicines for respiratory diseases such as acute bronchitis (Ajimura *et al*., 2018). A pharmacodynamic interaction occurs when two or more drugs work together to produce additive, synergistic, potentiated, or antagonistic effects at the same or connected receptors (Ajimura *et al*., 2018). A pharmacokinetic drug interaction occurs when a medication and/or its metabolite undergo changes in absorption, distribution, metabolism, and excretion (Ajimura *et al*., 2018). Pharmacokinetic drug interactions occur when one drug inhibits or induces the hepatic metabolism of another drug (Ajimura *et al*., 2018). For instance, when the inhaled corticosteroid (ICS) budesonide which is metabolized by the liver isoenzyme CYP P450 3A4, is given concurrently with a known inhibitor of CYP 3A4, such as the antifungal ketoconazole, a pharmacokinetic interaction occurs (Ajimura *et al*., 2018). Increased corticosteroid exposure is the result in this case, which might lead to adrenal suppression and/or weight gain (Ajimura *et al*., 2018).

The adverse effects caused by drug-drug interactions are unique such as changes in drug levels, increased risk of toxicity, additive anticholinergic effects, and corticosteroid accumulation with Cushing's syndrome (Ajimura *et al*., 2018). All prescribers should frequently examine and justify each patient's medication regimen, paying special attention to drug interactions (Ajimura *et al*., 2018). For the interpretation and management of possible medication interactions, pharmacists are a valuable resource (Ajimura *et al*.,

2018). This is a multidimensional process that entails assisting with medication selection, assessing every prescription order for potential interactions, conveying potential drug interactions to other members of the multidisciplinary team, and assisting with adverse reaction monitoring (Ajimura *et al.*, 2018).

1.9.2 The economic impact of irrational medicine use

An increasing number of authors reported that the irrational use of medicines for acute bronchitis has a great impact on the economy (Albert, 2010; Togoobaatar, 2010; Kinkade and Long, 2016). The World Health Organization (2010) disclosed that about US$ 300 billion of the annual worldwide health expenditure is wasted. The factors that lead to this loss of such a huge amount of money are irrational medicine use, poor financing administration, poor procurement procedures, and inadequate technical services (World Health Organization, 2010).

The irrational use of medicines such as antibiotics for acute bronchitis often leads to increased treatment costs which can put a financial burden on the patients (Albert, 2010; Kinkade and Long, 2016). The World Health Organization (2010) reported that about 10 – 40% of each national health budget is spent on purchasing medicines, so if medicines are not used rationally this can waste a lot of money for both personal and public funds.

1.9.3 Antimicrobial resistance

In the year 1928, Sir Alexander Fleming discovered the first antibiotic called penicillin at St Mary's Hospital in London (O'Neill, 2014). This became the basis of many of the greatest medical advances of the 20th century (O'Neill, 2014). However, Sir Fleming warned that if antibiotics are not used appropriately, antibiotic resistance which will cause more harm than good can occur (O'Neill, 2014). Burger *et al.* (2016) and O'Neill (2016) stated that antibiotics are substances used to treat bacterial infections and they act by killing or inhibiting the growth of bacteria. The Center for Disease Dynamics, Economics and

Policy (2015) reported that antibiotics have helped to prevent infections in many medical procedures such as surgery. Apart from lengthening the life span of humans, antibiotics can lead to antimicrobial resistance if they are not consumed rationally (Center for Disease Dynamics, Economics and Policy, 2015).

When a micro-organism is resistant to an antibiotic, the effectiveness of that antibiotic decreases and is therefore not sustained (Laxminarayan et al., 2016). In addition, the use of efflux pumps, the production of enzymes, genetic alterations, and the development of alternative pathways are some mechanisms through which microorganisms become resistant (van Wyk, 2015). Studies have documented that the effects of antimicrobial resistance include increased healthcare costs, prolonged hospital stays, and poor patient outcomes (World Health Organization, 2014; Centre for Disease Dynamics, Economics and Policy, 2015). Even though there are very few effective antibiotics left, many pharmaceutical companies are reluctant to conduct research on new antibiotics (Mabila *et al.*, 2016). Without effective antibiotics, surgical procedures such as organ transplantation and chemotherapy may become very risky (Messina *et al.*, 2017).

Antibiotic resistance is no longer a forecast for the future but rather a phenomenon that is occurring extensively worldwide and it requires an urgent solution (World Health Organization, 2014). The true impact of antibiotic resistance and its effect on patient outcomes is not properly understood in South Africa (Truter, 2015). If antibiotic use patterns are not monitored, more fatal diseases will emerge from multidrug-resistant microorganisms (Mabila *et al*., 2016).

1.10 Antimicrobial stewardship

Over time, extensive literature has developed on Antimicrobial Stewardship (AMS) which is part of the World Health Organization initiative to reduce antibiotic resistance (Boyles *et al.*, 2013; Dodds Ashley *et al.*, 2014; National Department of Health, 2014; File *et al.*, 2014; Brinkmann and Kibuule, 2019; Engler *et al.*, 2020). Antimicrobial stewardship policies have been made for all healthcare settings in South Africa to reduce antibiotic

resistance (National Department of Health, 2014; Engler *et al*., 2020). The main purpose of antimicrobial stewardship policies is to improve and standardize antibiotic use in all healthcare settings thus reducing antimicrobial resistance (National Department of Health, 2014). The standardization of antibiotic use can be obtained through regular monitoring and evaluation (Engler *et al*., 2020). According to File *et al.* (2014), antimicrobial stewardship programs can minimize adverse effects, improve patient outcomes, decrease hospital stay, minimize financial costs, and reduce antibiotic resistance.

Very little information exists in the literature regarding the effectiveness of antimicrobial stewardship strategies in South Africa (Boyles *et al.*, 2013). A healthcare provider plays a major role to ensure that antimicrobial stewardship policies are adhered to (National Department of Health, 2014). A good understanding of dispensing and prescribing patterns in primary care will enable antimicrobial stewardship interventions to be established (National Department of Health, 2014). Antimicrobial stewardship policies should ensure that no antibiotics are given for acute bronchitis (Frisina *et al.*, 2016). The adherence to antimicrobial stewardship policies in the treatment of acute bronchitis is not well understood in South Africa. The healthcare provider plays a big role in the establishment and monitoring of antimicrobial stewardship policies (Boyles *et al.*, 2013; Dodds Ashley *et al.*, 2014).

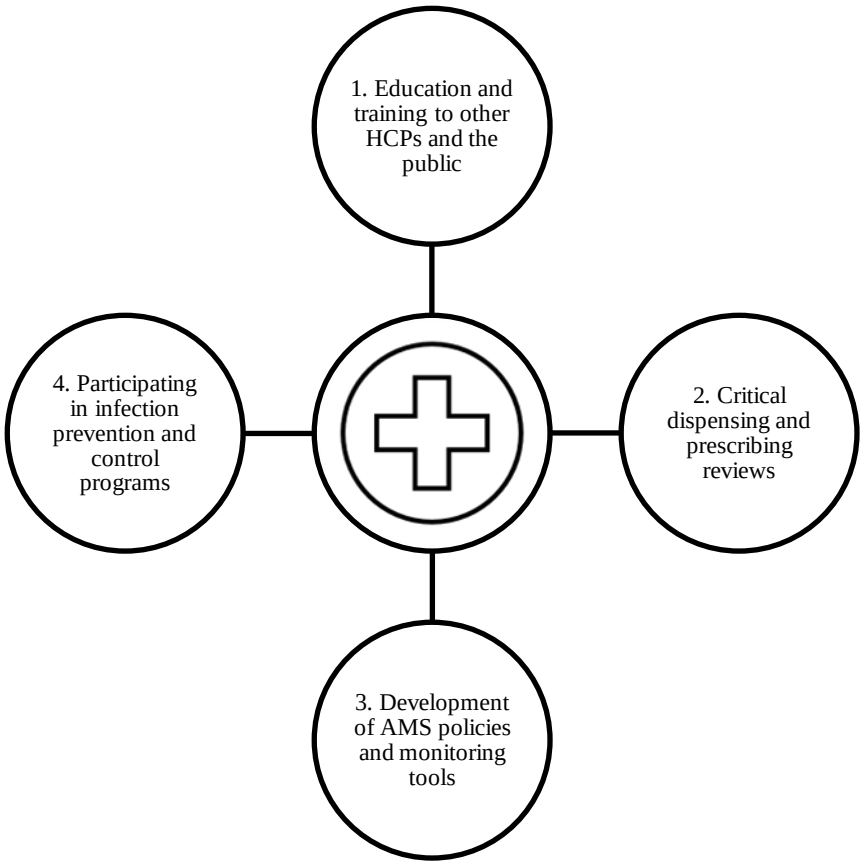

Figure 1.1: Role of the Healthcare Professional (HCP) in antimicrobial stewardship

1.11 Rationale of the Study

To date, there are very few publications on the medicines which are used to treat acute bronchitis in South African primary care and the level of adherence to evidence-based clinical practice guidelines is unknown.

From the literature search conducted, it is evident that the studies identified mostly focused on antibiotics and did not assess alternative therapies such as corticosteroids, opioids, and expectorants. Moreover, the studies on pharmacovigilance aspects of medicines given for acute bronchitis such as adverse effects caused by drug-drug interactions were very limited. Furthermore, there is limited data on investigations of the compliance to legislation by labels of dispensed medicines and prescriptions.

This highlights the importance of evaluating the prescribing patterns, dispensing practices, medicine utilization and legal aspects in the treatment of acute bronchitis in South African primary care so that problems can be identified, and interventions can be sought. Therefore, the research question for this study was: *Are prescribing practices, dispensing practices, medicine utilization and legal aspects in the treatment of acute bronchitis in primary healthcare settings in Johannesburg rational and adherent to evidence-based clinical practice guidelines?*

1.12 Aim

The aim of this study was to assess prescribing patterns, dispensing practices, medicine utilization and legal aspects in the treatment of acute bronchitis in both public primary healthcare settings, and private healthcare settings in Johannesburg.

1.13 Objectives

To obtain the above-mentioned aim, the following objectives were outlined:

1.13.1 To determine the prescribing patterns for acute bronchitis.

1.13.2 To determine the dispensing patterns for acute bronchitis.

1.13.3 To identify and classify the drug-drug interactions per patient visit.

1.13.4 To assess the level of compliance to legislation for the prescriptions.

1.13.5 To assess the level of compliance to legislation for the dispensed medicines.

1.14 Summary

In this chapter, a comprehensive literature review was undertaken on the background, epidemiology, definition, aetiology, pathophysiology, diagnosis, and treatment of acute bronchitis. Additionally, the dangers involved with irrational medicine use for acute bronchitis, antimicrobial stewardship policies, primary healthcare settings and legal requirements were discussed. The rationale of this study was also explained, followed by the aim and objectives. The next chapter will explain in detail the research methodology

used for conducting this study.

CHAPTER 2: RESEARCH METHODOLOGY

2.1 Introduction

This chapter will give a detailed explanation of the research methodology. This chapter will outline the study design, data sources, ethical considerations, data collection procedures, data analysis procedures, bias, reliability, and validity.

2.2 Study Design

This study was designed as a non-experimental quantitative, retrospective drug utilization study and was a secondary analysis of data previously collected. The data was previously collected in a study with the topic: Causal factors of antibiotic prescribing and patient-prescriber interactions in both public and private primary healthcare settings of South Africa (Appendix E). The preceding study's major aim was to explore how the interactions between prescribers and patients influence inappropriate antibiotic prescribing for acute respiratory tract infections in public and private primary care in South Africa (Appendix E).

The reason why this study was done is that the aim of the previous study and the aim of this study are entirely different. While the previous study aimed to assess the determinants of antibiotic prescribing in primary healthcare as well as patient-provider interactions, this study aimed to assess if the prescribing and dispensing practices in public and private primary healthcare settings are rational and adherent to guidelines. Additionally, the methodological approaches for both studies are completely different. The previous study used three methodological approaches which included an ethnographic study, online surveys, and visits by standardized patients. However, this research project had one methodological approach which was a retrospective drug utilization study.

Moreover, the research question and objectives for both studies are completely different. The objectives of the previous study focused on the perceptions and experiences of providers and patients about antibiotic prescribing for RTIs. However, the objectives for

this study focused on determining the prescribing patterns, dispensing patterns, drug-drug interactions, and compliance to legislation for acute bronchitis.

2.3 Data Sources

All the original data from the previous study was used for this study. The original data was obtained from 559 patient visits which were done in both private doctors' rooms and primary healthcare settings in Johannesburg, South Africa. The data sources were prescriptions and dispensed medicines that were obtained from the 559 patient visits done by standardized patients. These 559 visits were made by standardized patients to 186 private doctors and 73 public clinics in Johannesburg between 1 June 2018 and 31 August 2018. A standardized patient is an individual trained to act as a real patient by simulating a set of signs and symptoms to evaluate the clinical and communication skills of healthcare professionals (Plaksin *et al.*, 2016). The standardized patients simulated symptoms of acute bronchitis in each patient visit.

The standardized patients were part of the third methodological approach of the previous study. The standardized patients were of the same age, gender, weight, and health status. The standardized patients were trained to present with the same symptoms of acute bronchitis which included a cough. The visits were made in two phases. During the first phase, the standardized patients did not make any requests to the prescriber regarding the medication they were to receive. During the second phase, standardized patients expressed to the responsible healthcare professional that they did not want any antibiotics. The standardized patient presented with a cough at each visit and informed the healthcare provider that the cough had lasted for more than a week and it was not going away. The standardized patient also informed the healthcare provider that he or she had a blocked nose, a bit of a headache, sore throat, and runny nose which lasted for about 4 to 5 days in the previous week, but the cough was still present at the time of the visit.

There were 181 prescriptions obtained from the 181 patient visits in the private sector and the prescriptions were issued by a non-dispensing doctor (Figure 2.1). 798 medicines were dispensed by a dispensing doctor for 188 patient visits in the private sector and 454 medicines were dispensed by a primary healthcare nurse for 190 patient visits in the public

sector (Figure 2.1). All the prescriptions were obtained from the private sector while the dispensed medicines were obtained from both the private and public sectors (Figure 2.1).

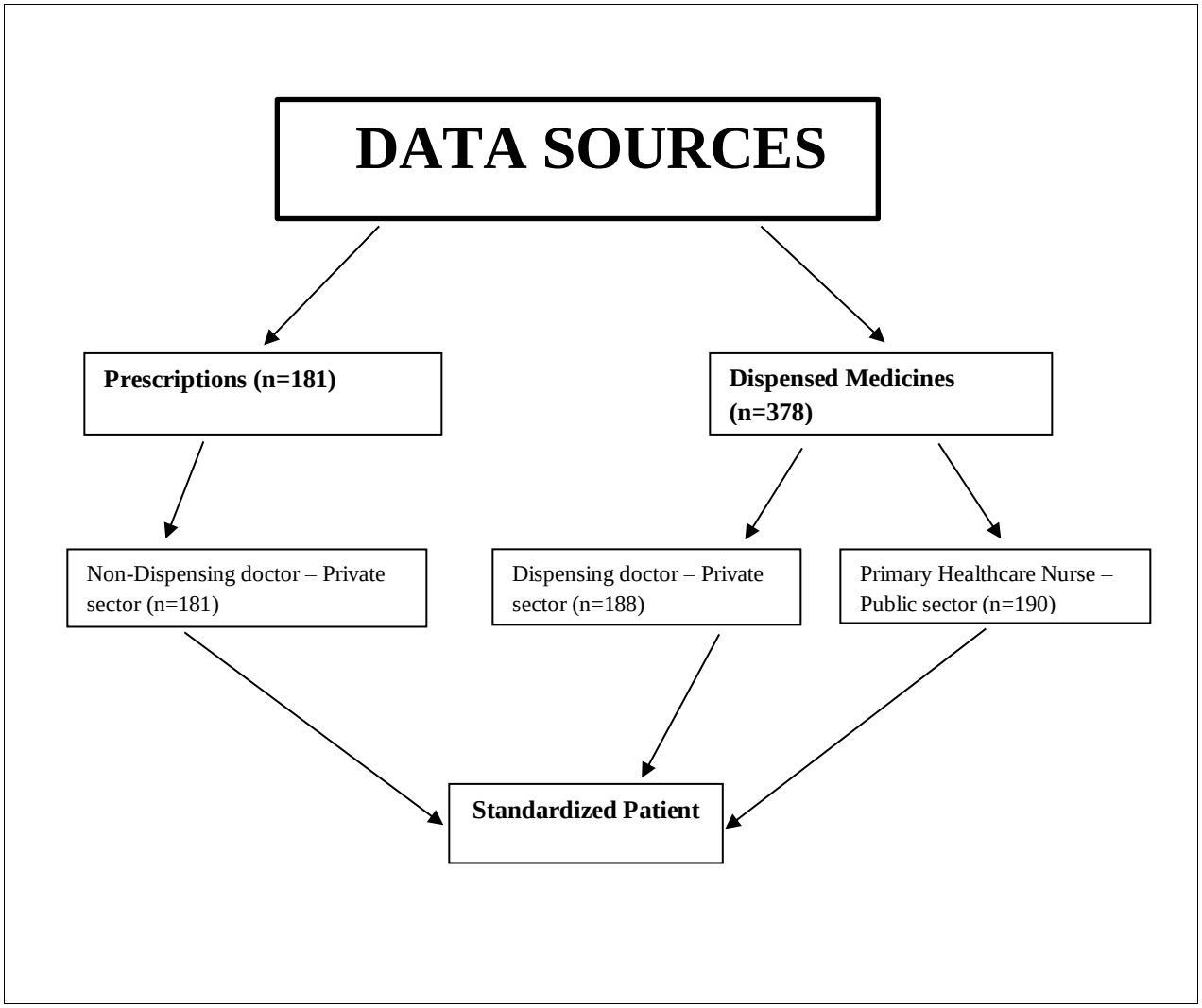

Figure 2.1: Data sources used for this study

2.4 Ethical Considerations

The previous study was conducted by three researchers from the Centre of Health Policy, University of the Witwatersrand, and the Department of Social Policy, London School of

Economics, and Political Science. The researchers from the previous study obtained permission to conduct their study from the Chief Director of the Johannesburg Health District, Gauteng Province to do their study in primary healthcare settings in Johannesburg (Appendix F). Their first ethical clearance certificate (M1611120) was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Appendix G). The Chair of the Research Ethics Committee at the London School of Economics and Political Science gave the second ethical approval (00513) for the previous study to be done (Appendix H).

The researchers from the previous study and the database keeper granted permission for their data sources to be used for this study (Appendix I). The ethics clearance certificate (M191085) for this study was granted by the Human Research Ethics Committee of the University of the Witwatersrand (Appendix J). In addition, an approval letter for this study was given by the Registrar of the Faculty of Health Sciences before it was conducted (Appendix K).

To ensure confidentiality, the names of the primary healthcare settings involved in this study will not be disclosed. In addition, this is to also protect the reputation of the participating primary healthcare settings if any negative findings regarding these facilities are obtained from this study. The 559 original data sources used for this study were accessed and kept in a safe and lockable office, from the 3rd floor of the School of Public health building at the University of the Witwatersrand. Moreover, a unique identifier for each visit was made called a Visit Identification Number (VID).

2.5 Data Collection Procedures

The Research Electronic Data Capture (REDCap) software was used to collect data for this study. REDCap is a web-based software developed by Vanderbilt University that is used for collecting, managing, and storing research data securely (Lyon *et al.*, 2014). Three data collection tools or instruments were designed and developed on REDCAP. These include Uploaded Entered Data (Appendix L), Validation Instrument (Appendix M), and Data

Entry (Appendix N). The REDCap project was moved to production status once the three data collection tools had been thoroughly tested, corrected, and finalized.

The Uploaded Entered Data tool was used to upload a data dictionary that had been created externally using Microsoft Excel 2016. However, for the Validation Instrument and the Data Entry tool, direct data entries were made on REDCap. The data collection was done at the Centre of Health Policy under the School of Public health, at the University of the Witwatersrand from the 1st of June 2020 to the 2nd of July 2020. The prescriptions and dispensed medicines were accessed in a safe and lockable office on the third floor at the WITS School of public health.

2.5.1 Prescription data collection

The prescriptions were all arranged in yellow files which were kept in a safe and lockable office on the third floor at the WITS School of Public health. Each prescription had a Visit Identification Number (VID) which was used to identify each prescription. During data collection, one prescription was taken at a time from a file for assessment. A prescription was first analysed for its legality and authenticity. Firstly, the Uploaded entered data (Appendix L) tool was used to check and see if the medicines written on the prescription were the ones on the uploaded data. If there were any mistakes, the Validation tool (Appendix M) was used to make this correction. For instance, if the uploaded data had a quantity of twenty for Prednisone 5mg tablets while the actual quantity on the prescription was thirty, this would be corrected using the Validation tool and thirty would be written to replace twenty. A data entry tool (Appendix N) which had been made in REDCap with variables specific to a prescription, was used to collect data. Each variable was entered at a time. The data collector sat through all the prescriptions until data had been collected for all the prescriptions. Table 2.1 shows a list of variables used for collecting data from the prescriptions.

After the data had been collected, each prescription was returned into the respective file and arranged accordingly. A total of 181 prescriptions were found in this study and these had a total of 537 medicines that were prescribed by a non-dispensing doctor. The data collected for prescriptions were used to establish the prescribing patterns for viral

bronchitis and it was also used to assess the level of compliance to the legislation of a prescription.

2.5.2 Medicine packet data collection

The dispensed medicines for each patient visit were put in a medicine packet which was in turn, put into a green file. The green files with medicine packets were all kept in a safe and lockable office on the third floor at the WITS School of Public health. Each medicine packet had a Visit Identification Number (VID) which was used for identification purposes. One medicine packet was taken at a time for assessment. Each medicine packet either had the medicine in the original container from the manufacturer or the medicine in a patient-ready pack that had undergone pre-packing. One medicine packet was opened at a time and the parameters on the label were assessed. Firstly, the Uploaded entered data (Appendix L) tool was used to check and see if the dispensed medicines were the ones recorded on the uploaded data. If there were any mistakes, the Validation tool (Appendix M) was used to make this correction. For instance, if the uploaded data had a strength of 20mg for Prednisone tablets while the actual strength on the label of the dispensed medicine was 5mg, this would be corrected using the Validation tool and 5mg would be written to replace 20mg. The data collector sat through all the medicine packets until all the data had been collected.

After data collection of each medicine packet, it was returned to its respective file and arranged accordingly in order, to avoid mix-ups. The data collected included the following: in the private sector, 70% (n=559) of the medicines had been dispensed in their original containers and 30% (n=239) of the medicines had undergone pre-packing and dispensed in patient-ready packs. In the public sector, 40% (n=182) of the medicines had been dispensed in their original containers and 60% (n=272) of the medicines had undergone pre-packing and dispensed in patient-ready packs. The data collected on dispensed medicines was used to determine the dispensing patterns and to assess the level of compliance to legislation for labels of dispensed medicines. Table 2.1 below: shows all the variables which were used to collect data for this study, and which are also shown on the three REDCap data collection tools (Appendix L, Appendix M, and Appendix N).

Table 2.1: Data indicators and/or variables

Data Indicators and/or Variables	**Reason for inclusion in the study**
Visit Identification Number referred to as VID	To identify data sources and maintain confidentiality
Date of Data Collection	To know when the data was entered for each data source
Script identity	To identify what each data source represented either a prescription or a dispensed medicine for comparisons
Group	To identify a group of data sources that were obtained by one standardized patient or the number of patient visits that were made by a particular standardized patient
Sector	To compare results of this study between the public and private sectors
Dose: Defined Daily Dose (DDD)	To ascertain the level of adherence to standard treatment guidelines by assessing if the dose given for each medicine was in alignment with the DDD
Dosage intervals/Dosing frequency	To ascertain the level of adherence to standard treatment guidelines by assessing if the correct dosage intervals had been given for each medicine
Duration of Therapy	To ascertain the level of adherence to standard treatment guidelines by assessing if the correct duration of therapy had been given for the medicine
Quantity	To ascertain the level of adherence to standard treatment guidelines by assessing if the correct quantity of the medicine had been given
Variables for the Uploaded Entered Data Tool	These variables were used to check if what was recorded on the uploaded data dictionary was on the prescription or in the medicine packet. These variables were duplicated eight times

	in order, to allow data collection for up to eight drugs per data source or patient visit. The variables were: 1. drug1 script 2. drug1 name 3. drug1 NAPPI code 4. drug1 active ingredient 5. drug1 strength 6. drug1 unit 7. drug1 format 8. drug1 form/dosage form 9. drug1 pack 10. drug1 schedule 11. drug1 quantity 12. drug 1 ATC code
Variables for the Validation tool	These variables were used to validate the uploaded data and confirm if what was recorded on the uploaded data dictionary was on the prescription or in the medicine packet. For instance, if the uploaded data had a mistake, this mistake would be corrected on the validation instrument. Since the uploaded data showed a maximum of seven drugs per data source or patient visit, the variables for the validation instrument were duplicated seven times in order, to allow data collection for up to seven. The variables were fewer than those of the uploaded entered data tool, except that there was an additional variable called ‘‘checked’’, which indicated if that record had been validated or not. The variables were: 1. drug1 script 2. drug1 name 3. drug1 NAPPI code

	4. drug1 strength 5. drug1 unit 6. drug1 form/dosage form 7. drug1 quantity 8. checked
Variables for a label on the original container of a dispensed medicine	To evaluate the compliance to the legislation of a label for a dispensed medicine, the following variables were required: 1. Approved name, or the name of each active ingredient of the medicine 2. Name of the patient 3. Directions of use 4. Reference number 5. Name of the dispenser 6. The business address of the dispenser 7. Dispensing date N.B: All the medicines which were dispensed in their original containers had certain labelling parameters on the original containers from the manufacturers and not on the label. These labelling parameters are as follows: registration number, dosage form, name of preservative, batch number, and expiry date.
Variables for the label of a dispensed medicine which was repacked	To evaluate the compliance to the legislation of a label for a dispensed medicine that has undergone pre-packing, the following variables were required: 1. batch number 2. packaging date or dispensing date 3. the approved name of the medicine

	4. the strength 5. the quantity or volume of medicine 6. the expiry date, 7. the name of the packaging institution 8. the address of the packaging institution 9. any necessary additional information, i.e., storage conditions and warnings. 10. directions of use 11. name of the patient 12. reference number
Variables for a prescription	To evaluate the compliance to the legislation of a prescription, the following fields were required: 1. Prescription date 2. Patient's identification number 3. Patient's name 4. Patient's address 5. Patient's age 6. Patient's gender 7. Prescriber's name 8. Prescriber's qualifications 9. Prescriber's registration number/MP number 10. Prescriber's address 11. Prescriber's contact details 12. Approved name of medicine 13. Dosage form 14. Strength 15. Quantity 16. Instructions for use, including the dose and frequency of administration 17. Prescriber's signature: handwritten

Number of antibiotics	To determine the frequency, to evaluate the level of adherence to guidelines, and for comparisons
Number of drugs	To determine the frequency of the number of drugs, to evaluate the level of adherence, and for comparisons
Drug-drug interaction	To identify, classify and compare the drug-drug interactions, Drug-to-drug interactions had to be categorized into three different types which are minor, moderate, and serious using the Medscape interactions checker.
Number of drug-drug interactions	To determine the frequency of the drug-drug interactions and for comparisons
Name of interacting drug 1	To know the class and name of one of the interacting drugs for each drug-drug interaction
Name of interacting drug 2	To know the class and name of one of the interacting drugs for each drug-drug interaction
Type of drug-drug interaction	To know the type of drug-drug interaction and the severity, if it was minor, moderate, or serious
Explanation of drug-drug interaction	To know the explanation for each drug-drug interaction, if it was an antagonistic action or if it was an increase in the risk of toxicity

After the data collection was completed, data exports were made from REDCAp and exported as csv files to Microsoft Excel 2016. In Microsoft Excel 2016, the csv files were converted into xlsx files. The variables were identified either as categorical or continuous. Data cleaning was done in Microsoft Excel 2016 to ensure that the data was correct, easy to use, and consistent. If any errors were found in the data, they were corrected or removed.

2.6 Data Analysis Procedures

The data analysis was carried out using STATA version 15 software. Firstly, the xlsx file with the data was imported onto STATA. The variables were identified either as categorical or continuous. The Data [Editor] Browse tool was used to check if the imported data was

correct before the data analysis began. Any errors found were corrected using the Data [Editor] Edit tool in STATA. All commands for the data analysis were typed in the command window in STATA.

Descriptive statistics were used to summarize the research findings of this study. The count, mean, minimum and maximum were used to summarize the continuous variables. Frequency counts, percentages, cumulative frequencies, one-way and two-way tables were used to summarize categorical variables. Stacked Column charts were used to represent categorical variables graphically.

Table 2.2: Statistical analyses and graphical illustrations obtained from STATA 15

Type of Variable	**Statistical analysis**	**Graphical illustrations**
Continuous (Normally distributed) variables	N, mean, minimum, maximum	Column charts and Histograms
Continuous (skewed) variables	N, median, minimum, maximum	Column charts and Histograms
Categorical variables	Frequency counts, percentages (one-way tables, two-way tables)	Stacked Column charts

The Shapiro-Wilk test, as well as the Skewness and kurtosis normality test, were used to evaluate if the continuous variables followed a normal distribution. These two tests for normality revealed that all the continuous variables for this study did not follow a normal distribution but were skewed. The Chi-square test was performed in order, to compare the rate of public sector vs private sector's compliance with each of the labelling requirements. A p-value of less than 0.05 was regarded statistically significant.

All the medicines given in this study were classified using the ATC codes of the World Health Organization (WHO). The Anatomical Therapeutic Chemical (ATC) classification is a reputable classification system for medicines that is maintained by the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2020). The WHO assigns ATC codes to all active ingredients contained in medicines (WHO, 2020). The motive for using the ATC codes was to examine the quality of drug use through classifying therapeutic drugs into distinct groups, according to their therapeutic, chemical, and pharmacological properties as well as the system or organ on which they act (WHO, 2020).

The Defined Daily Dose (DDD) of the World Health Organization was a very important tool that was used to assess the level of adherence to guidelines for all the medication used for this study (WHO,2020). The DDD is a statistical measure of drug utilization or consumption, and it was established by the Centre for Drug Statistics and Methodology of the World Health Organization (WHO, 2020). The DDD is defined as the assumed average daily maintenance dose for a drug when used for its main indication in adults (WHO, 2020). The DDD is used in combination with the ATC code classification system, and it enables the comparison of drug usage for different drugs in the same class or between different healthcare settings (WHO, 2020).

The Medscape database or Medscape interactions checker was used to identify potential drug-drug interactions, the possible adverse drug reactions, and the clinical significance of these interactions (Medscape, 2020). A computer and internet access were needed to identify drug-drug interactions using the Medscape database or Medscape interactions checker. For all the drug-drug interactions, the Medscape interactions checker was used to categorize them into three categories which were serious, monitor closely/moderate, and minor (Medscape, 2020).

The interaction was categorized as, ‘‘serious’’, if the interaction would put the patient’s life at risk or cause permanent damage (Medscape, 2020). The interaction was categorized as, ‘‘moderate or monitor closely’’, if it could cause a deterioration in the patient’s health condition that may require additional therapy (Medscape, 2020). The interaction was categorized as, ‘‘minor’’, if it had no significant clinical involvement or if it was a slight interaction (Medscape, 2020). The Medscape Interactions checker also gave a detailed

explanation for each type of drug-drug, interaction, for instance, antagonistic action (Medscape, 2020). The drug-drug, interactions were also grouped according to them being in the private sector or public sector, and the comparisons were made.

2.7 Bias

In research, bias is described as an unjust and prejudiced preference for one concept, solution, outcome, person, or group over another (Krishna *et al*., 2010). Randomization is a method used to reduce bias in research and it helps to ensure that different groups will be comparable with respect to known and unknown variables (Krishna *et al.*, 2010). Randomization was used to reduce reader-order bias in this study when reviewing the data sources retrospectively. Bias was also avoided by recognizing that the acceptance of the hypothesis should not be the goal of the study because when a researcher is determined to get his or her hypothesis accepted, he or she will employ biased and prejudiced methods to do so. Since this was a quantitative study, the chi-square statistical test was used to ensure that there was no bias by determining the authenticity and integrity of the results. All the original data sources were used for this study to ensure that there was no bias and that authentic results would be obtained. Consecutive recruitment was used to avoid bias in this study by ensuring that no characteristics that were not in proportion with the study population were inadvertently introduced.

2.8 Reliability and Validity

To ensure validity and reliability, the research supervisors would double-check all the data as it was being collected by the principal investigator. Validity is defined as the degree to which a certain measurement is accurate (Leedy and Ormrod, 2005). Reliability means the consistency with which a measuring instrument yields a particular result (Leedy and Ormrod, 2005). Additionally, the data collected was verified by a qualified pharmacist who assisted the researcher in the interpretation of the information thus ensuring accuracy.

The data collected was validated electronically by REDCap using the Validation Instrument (Appendix M) to check if the entered data was correct and in alignment with

the uploaded data. A pilot study for twenty prescriptions, twenty labels of dispensed medicines in original containers, and twenty labels of dispensed medicines that had been repacked was done on REDCap. The pilot study was done for ensuring the reliability of the study and determining the consistency with which the data collection instruments yielded results when collecting data.

2.9 Summary

This chapter discussed the research methodology that was used to obtain the objectives for this study. The study design, study setting, ethical considerations, data sources, data collection procedures, and data analysis procedures were described. The following chapter will focus on the research findings for this study.

CHAPTER 3: RESULTS

3.1 Introduction

This chapter outlines the results obtained from this study. Prescribing patterns, dispensing patterns, drug-drug interactions, compliance to legislation for a prescription, and compliance to the legislation of a label for a dispensed medicine are the headings used to report this chapter. The results of this study will focus on the prescribing patterns, dispensing practices, medicine utilization, and legal aspects in the treatment of acute bronchitis, in both public and private primary healthcare settings in Johannesburg. There were 181 prescriptions obtained from the 181 patient visits in the private sector, and the prescriptions were issued by a non-dispensing doctor. Seven-hundred and ninety-eight medicines were dispensed by a dispensing doctor for 188 patient visits in the private sector and 454 medicines were dispensed by a primary healthcare nurse for 190 patient visits in the public sector. All the prescriptions were obtained from the private sector while the dispensed medicines were obtained from both the private and public sectors

3.2 Prescribing patterns for acute bronchitis

A total of 537 drugs were prescribed by non-dispensing doctors from the private sector (Table 3.1). The prescribers for all the drugs issued a total of 181 prescriptions (Table 3.1). Generics prescribed exceeded originators, i.e., 60.3% (n=324) vs 39.7% (n=213) (Table 3.1).

Table 3.1: A summary of results from the prescriptions in the private sector

Category	**Frequency**
Number of prescriptions	181
Total number of drugs	537 (100%)
Total number of generics	324 (60.3%)
Total number of originators	213 (39.7%)
Minimum number of drugs on each	1

prescription	
Maximum number of drugs on each prescription	7
The average number of drugs on each prescription	4

The total 537 medicines prescribed in this study were classified using the ATC codes from the World Health Organization (Appendix O). Combination drugs, also known as other cold preparations, had the highest percentage of 29.8% (n=160) (Table 3.2). The results show that 96.6% (n=519) of all the prescribed medicines had a dose that was in alignment with the Defined Daily Dose (DDD) and 95.7% (n=514) had their dosage intervals provided (Table 3.2). In addition, almost half of the prescribed drugs, i.e., 48.2% (n=259) of all the prescribed drugs did not provide the duration while 32.6% (n=175) lacked the quantity needed (Table 3.2).

Table 3.2: Prescribing patterns for acute bronchitis in the private sector

Drug class	**n (%)**	**Category**	**Defined Daily Dose (DDD)**	**Dosage Intervals**	**Duration**	**Quantity**
Total number of drugs	537 (100%)	C	519 (96.6%)	514 (95.7%)	278 (51.8%)	362 (67.4%)
		NC	18 (3.4%)	23 (4.3%)	259 (48.2%)	175 (32.6%)
Combination drugs	160 (29.8%)	C	159 (99.4%)	159 (99.4%)	83 (51.9%)	111 (69.4%)
		NC	1 (0.6%)	1 (0.6%)	77 (48.1%)	49 (30.6%)
Corticosteroids	112 (20.8%)	C	100 (89.3%)	100 (89.3%)	59 (52.7%)	77 (68.8%)
		NC	12 (10.7%)	12 (10.7%)	53 (47.3%)	35 (31.2%)
Antibiotics	109 (20.3%)	C	108 (99.0%)	108 (99.0%)	57 (52.3%)	75 (68.8%)
		NC	1 (1.0%)	1 (1.0%)	52 (47.7%)	34 (31.2%)
Antihistamines	54 (10.0%)	C	54 (100%)	54 (100%)	29 (53.7%)	38 (70.4%)
		NC	0 (0%)	0 (0%)	25 (46.3%)	16 (29.6%)
Complementary medicines	22 (4.1%)	C	22 (100%)	22 (100%)	12 (54.5%)	16 (72.7%)

		NC	0 (0%)	0 (0%)	10 (45.5%)	6 (27.3%)
Other drugs	80 (15.0%)	C	76 (95.0%)	76 (95.0%)	38 (47.5%)	45 (56.3%)
		NC	4 (5.0%)	4 (5.0%)	42 (52.5%)	35 (43.7%)
*C – Compliant **NC – Non-compliant N.B: Refer to Appendix O for more details on the prescribed medicines in the private sector						

The drug classes which had lower frequencies were grouped into one category called other drugs (Table 3.2). Oseltamivir, a neuraminidase inhibitor, was the only antiviral prescribed in this study (Appendix O). Some of the medicines that were prescribed are not indicated for acute bronchitis and these include imidazole antifungals, Proton Pump Inhibitors (PPIs), Angiotensin-Converting Enzyme Inhibitors (ACEI), and Combined Oral Contraceptives (COCs) (Appendix O).

3.3 Dispensing patterns for acute bronchitis

A total of 798 drugs were dispensed in the private sector by a dispensing doctor while a total of 454 drugs were dispensed in the public sector by a PHC nurse (Table 3.3). The results included the following: in the private sector, 70% (n=559) of the medicines had been dispensed in their original containers and 30% (n=239) of the medicines had undergone pre-packing and dispensed in patient-ready packs. In the public sector, 40% (n=182) of the medicines had been dispensed in their original containers, and 60% (n=272) of the medicines had undergone pre-packing and dispensed in patient-ready packs. The minimum number of drugs dispensed per patient visit was 1 both in the private and public sectors (Table 3.3). The maximum number of drugs dispensed per patient visit was higher in the private sector, i.e., 7, while in the public sector it was lower, i.e., 4 (Table 3.3). All the drugs given in the public sector were generics as expected, while the originator drugs were exclusive to the private sector (Table 3.3).

Table 3.3: A summary of dispensed medicines from both sectors

Category	**Primary Healthcare Nurse (Public Sector-**	**Dispensing doctor (Private Sector-Dispensed)**

	Dispensed)	
Total number of drugs	454 (100%)	798 (100%)
Total number of generics	454 (100%)	576 (72.2%)
Total number of originators	0 (0%)	222 (27.8%)
Minimum number of drugs dispensed for each patient visit	1	1
Maximum number of drugs dispensed for each patient visit	4	7
The average number of drugs dispensed for each patient visit	3	4

The dispensing patterns of dispensing doctors (Table 3.4) showed that combination drugs, i.e., 44.4% (n=354) were the mostly prescribed followed by antibiotics at 19.1% (n=152). Vitamins, i.e., 1.5% (n=12) were not commonly dispensed by the private dispensing doctors. Three pharmacological classes were grouped into one class called analgesics and these include opioids, Non-Steroidal Anti-inflammatory Drugs (NSAIDS), and aniline analgesics. Aniline analgesics accounted for 5.1% (n=41), NSAIDs accounted for 4.1% (n=33) and opioids accounted for 1.6% (n=13) (Table 3.4). The non-compliance to providing the duration and quantity of drugs exceeded 85% in both (Table 3.4). All the drug classes which had a frequency of less than ten from dispensed medicines in the private sector were grouped into a category called other drugs (Appendix O).

Table 3.4: Dispensing patterns by Dispensing doctors in the private sector

Drug class	**n (%)**	**Category**	**Defined Daily Dose (DDD)**	**Dosage Intervals**	**Duration**	**Quantity**
Total number of drugs	798 (100%)	C	798 (100%)	798 (100%)	18 (2.6%)	117 (14.7%)
		NC	0 (0%)	0 (0%)	780 (97.4%)	681 (85.3%)

Combination drugs	354 (44.4%)	C	354 (100%)	354 (100%)	9 (2.5%)	53 (15.0%)
		NC	0 (0%)	0 (0%)	345 (97.5%)	301 (85.0%)
Antibiotics	152 (19.0%)	C	152 (100%)	152 (100%)	4 (2.6%)	23 (15.1%)
		NC	0 (0%)	0 (0%)	148 (97.4%)	129 (84.9%)
Corticosteroids	108 (13.6%)	C	108 (100%)	108 (100%)	3 (2.8%)	16 (14.8%)
		NC	0 (0%)	0 (0%)	105 (97.2%)	92 (85.2%)
Analgesics	87 (10.8%)	C	87 (100%)	87 (100%)	1 (1.2%)	13 (14.9%)
		NC	0 (0%)	0 (0%)	86 (98.8%)	74 (85.1%)
Antihistamines	45 (5.6%)	C	45 (100%)	45 (100%)	1 (2.2%)	7 (15.6%)
		NC	0 (0%)	0 (0%)	44 (97.8%)	38 (84.4%)
Xanthines	12 (1.5%)	C	12 (100%)	12 (100%)	0 (0%)	2 (16.7%)
		NC	0 (0%)	0 (0%)	12 (100%)	10 (83.3%)
Vitamins	12 (1.5%)	C	12 (100%)	12 (100%)	0 (0%)	1 (8.3%)
		NC	0 (0%)	0 (0%)	12 (100%)	11 (91.7%)
Other drugs	28 (3.6%)	C	28 (100%)	28 (100%)	0 (0%)	2 (7.1%)
		NC	0 (0%)	0 (0%)	28 (100%)	26 (92.9%)

*C – Compliant
**NC – Non-compliant

N.B: Refer to Appendix O for more details on the dispensed medicines in the private sector

In primary healthcare, the duration (99.6%) and quantity (91.0%) of the dispensed medicines were missing (Table 3.5). Antibiotics, i.e., 31.1% (n=141) was the most prescribed drug class followed by analgesics at 30.0% (n=136) (Table 3.5). The analgesics in the PHC setting commonly used paracetamol at 28.0% (n=127), while NSAIDs comprised of only 2.0% (n=9) (Table 3.5). Combination drugs in the PHC setting featured much lower at 1.3% (n=6) compared to the other drugs while the vitamins were more common in this group at 15.4% (Table 3.5).

Table 3.5: Dispensing patterns by PHC nurses in the public sector

Drug class	n (%)	Category	Defined Daily Dose (DDD)	Dosage Intervals	Duration	Quantity
Total number of drugs	454 (100%)	C	420 (92.5%)	413 (91.0%)	2 (0.4%)	41 (9.0%)
		NC	34 (7.5%)	41 (9.0%)	452 (99.6%)	413 (91.0%)
Antibiotics	141 (31.1%)	C	129 (91.5%)	129 (91.5%)	1 (0.7%)	14 (9.9%)
		NC	12 (8.5%)	12 (8.5%)	140 (99.3%)	127 (90.1%)
Analgesics	136 (30.0%)	C	124 (91.2%)	124 (91.2%)	1 (0.7%)	12 (8.8%)
		NC	12 (8.8%)	12 (8.8%)	135 (99.3%)	124 (91.2%)
Antihistamines	85 (18.7%)	C	79 (93.0%)	79 (93.0%)	0 (0%)	8 (9.4%)
		NC	6 (7%)	6 (7%)	85 (100%)	77 (90.6%)
Vitamins	70 (15.4%)	C	70 (100%)	64 (91.4%)	0 (0%)	7 (10.0%)
		NC	0 (0%)	6 (8.6%)	70 (100%)	63 (90.0%)
Nasal decongestants	9 (2.0%)	C	7 (77.8%)	7 (77.8%)	0 (0%)	0 (0%)
		NC	2 (22.2%)	2 (22.2%)	9 (100%)	9 (100%)
Corticosteroids	6 (1.3%)	C	5 (83.3%)	5 (83.3%)	0 (0%)	0 (0%)
		NC	1 (16.7%)	1 (16.7%)	6 (100%)	6 (100%)
Combination drugs	6 (1.3%)	C	5 (83.3%)	5 (83.3%)	0 (0%)	0 (0%)
		NC	1 (16.7%)	1 (16.7%)	6 (100%)	6 (100%)
Short-acting beta agonists	1 (0.2%)	C	1 (100%)	0 (0%)	0 (0%)	0 (0%)
		NC	0 (0%)	1 (100%)	1 (100%)	1 (100%)

* C – Compliant
**NC – Non-compliant

NSAIDs – Non-Steroidal Anti-inflammatory Drugs

N.B: Refer to Appendix O for more details on the dispensed medicines in the public sector

All the medicines dispensed in the private sector by dispensing doctors, i.e., 100% (n=798), had a dose that was in alignment with the Defined Daily Dose (DDD) of the World Health Organization (Table 3.4). However, in the public sector, 92.5% (n=420) of all the drugs had a dose that was in alignment with the DDD (Table 3.5).

3.4 Drug-drug interactions

The drug-drug interactions were identified for each sector and categorized into three types which are minor, monitor closely/moderate and serious as per the Medscape interactions checker (Table 3.6). The medicines dispensed in the private sector had the highest number of drug-drug interactions (Figure 3.1; Table 3.6). The dispensed medicines from the private sector had a total of 341 interactions including 7.6% (n=26) minor interactions, 87.4% (n=298) moderate interactions and 5.0% (n=17) serious interactions (Figure 3.1; Table 3.6).

The prescribed medicines in the private sector had the second-highest number of interactions (Figure 3.1; Table 3.6). The prescribed medicines from the private sector had a total of 129 interactions including 6.2% (n=8) minor interactions, 85.3% (n=110) moderate interactions and 8.5% (n=11) serious interactions (Figure 3.1; Table 3.6). The public sector had the lowest number of interactions, i.e., 27 including 51.9% (n=14) minor interactions, 48.1% (n=13) moderate interactions and it had no interactions in the serious category (Figure 3.1; Table 3.6).

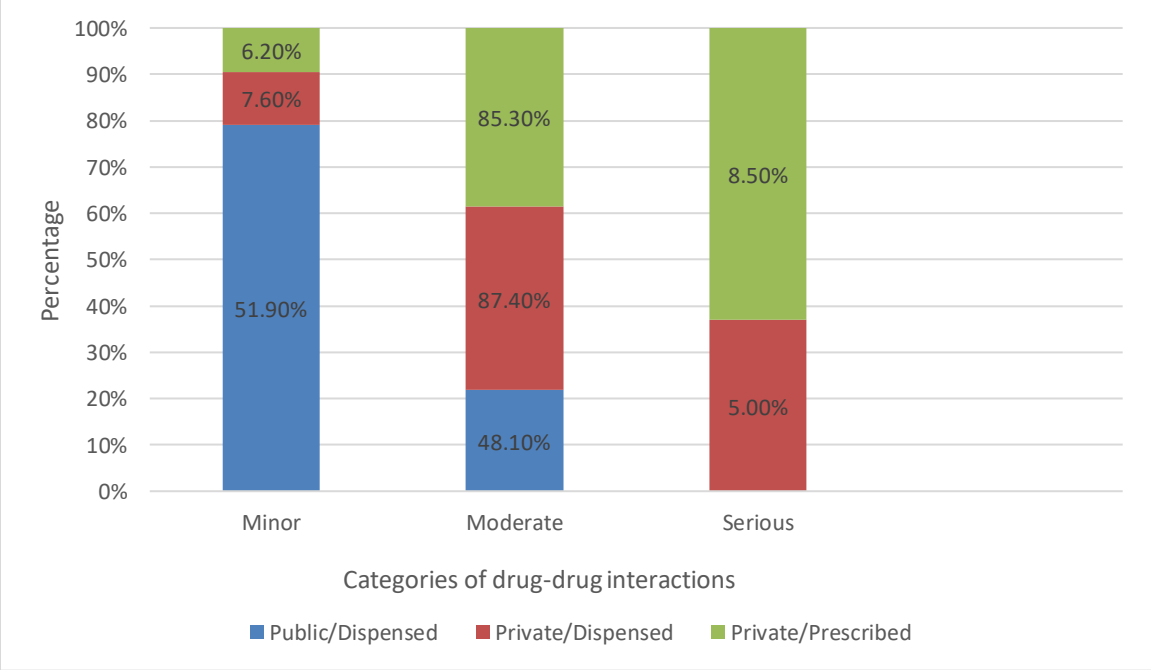

Figure 3.1: Categories of drug-drug interactions

The minimum number of drug-drug, interactions was 1 for all sectors (Table 3.6). The dispensed medicines from the private sector had the highest average number of interactions per patient visit which was 5 (Table 3.6). The maximum number of interactions was 4 for dispensed medicines in the public sector, 8 for the dispensed medicines in the private sector, and 6 for prescribed medicines in the private sector (Table 3.6).

Table 3.6: Statistics for interactions per patient visit

Category	**Non-dispensing doctor (Private sector – prescribed)**	**Dispensing doctor (Private sector - dispensed**	**PHC nurse (Public sector – dispensed)**
Minimum number of drug-drug, interactions	1	1	1
Maximum number of drug-drug, interactions	6	8	4
The average number of drug-drug interactions	3	5	3
Number of minor drug-drug interactions	8 (6.2%)	26 (7.6%)	14 (51.9%)
Number of moderate drug-drug interactions	110 (85.3%)	298 (87.4%)	13 (48.1%)
Number of serious drug-drug interactions	11(8.5%)	17 (5.0%)	0 (0%)

The types of drug-drug interactions were grouped into categories for each sector (Table

3.7; Table 3.8; Table 3.9). The frequency and percentage for each type were evaluated and recorded (Table 3.7; Table 3.8; Table 3.9). In addition, the interacting drugs were grouped per pair and the frequencies, as well as percentages of each pair, were recorded (Appendix P).

The type of interaction with the highest percentage for prescribed medicines in the private sector was the increased sedation category at 45.8% (n=59) (Table 3.7). Types of interactions with very low percentages were grouped as other interactions and these include: levels of one drug increased due to renal excretion at 4.7% (n=6), levels of one drug decreased due to absorption at 3.1% (n=4), levels of one drug increased due to absorption at 3.1% (n=4), levels of one drug decreased by the other drug directly at 1.5% (n=2), levels of one drug decreased due to protein binding at 0.8% (n=1) and levels of one drug decreased due to renal excretion at 0.8% (n=1) (Table 3.7).

Table 3.7: Types of interactions between prescribed medicines in the private sector

Type of Drug-drug interaction	**Frequency**	**Percentage**
Antagonistic action	22	17.0%
Increased risk of toxicity	7	5.4%
Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug	11	8.5%
Levels of one drug increased due to metabolic enzymes with increased effects of the drug	12	9.3%
Increased sedation	59	45.8%
Other interactions	18	14.0%
Total	129	100%
N.B: Refer to Appendix P for more details on the drug-drug interactions between prescribed medicines in the private sector		

The type of interactions with the highest percentage for dispensed medicines in the private

sector was the antagonistic action category at 40.8% (n=139) (Table 3.8). Types of interactions with very low percentages were grouped as other interactions and these include: levels of one drug increased due to renal excretion at 0.6% (n=2), levels of one drug decreased due to absorption at 1.7% (n=6), levels of one drug increased due to absorption at 0.6% (n=2), levels of one drug decreased by the other drug directly at 2.6% (n=9), levels of one drug decreased due to protein binding at 0.6% (n=2), levels of one drug decreased due to renal excretion at 0.3% (n=1), levels of one drug decreased by another drug directly at 0.3% (n=1) and levels of one drug increased with increased risk in toxicity at 0.3% (n=1) (Table 3.8).

Table 3.8: Types of interactions between dispensed medicines in the private sector

Type of Drug-drug interaction	**Frequency**	**Percentage**
Antagonistic action	139	40.8%
Increased risk of toxicity	14	4.1%
Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug	41	12.0%
Levels of one drug increased due to metabolic enzymes with increased effects of the drug	28	8.3%
Increased sedation	95	27.8%
Other interactions	24	7.0%
Total	341	100%
N.B: Refer to Appendix P for more details on the drug-drug interactions between dispensed medicines in the private sector		

The type of interactions with the highest percentage for dispensed medicines in the public sector was the levels of one drug decreased due to absorption at 81.5% (n=22) (Table 3.9). Three types each had the lowest percentage at 3.7% (n=1) (Table 3.9).

Table 3.9: Types of interactions between dispensed medicines in the public sector

Type of Drug-drug interaction	Frequency	Percentage
Antagonistic action	1	3.7%
Increased risk of toxicity	1	3.7%
Levels of one drug decreased by the other drug directly	2	7.4%
Levels of one drug decreased due to absorption interactions	22	81.5%
Increased sedation	1	3.7 %
Total	27	100%
N.B: Refer to Appendix P for more details on the drug-drug interactions between dispensed medicines in the public sector		

It is very concerning that serious drug-drug interactions which may cause severe damage to the patient were observed in this study. The Medscape database or Medscape interactions checker was used to identify potential drug-drug interactions, and the interaction was categorized as, ‘‘serious’’, if the interaction would put the patient’s life at risk or cause permanent damage (Medscape, 2020). The serious drug-drug interactions observed in this study is given in Table 3.10 below. The serious drug-drug interactions were not observed in the public sector, but only in the private sector.

Table 3.10: Serious drug-drug interactions

Interacting pair of medicines	Sector/ Healthcare Professional (HCP)	Category	Explanation	Frequency
PRESCRIBED MEDICINES IN THE PRIVATE SECTOR				
1. Erythromycin /Theophylline	Private/Non-dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Erythromycin will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.	5
2. Prednisone /Erythromycin	Private/Non-dispensing doctor	Levels of one drug increased due to metabolic enzymes	Erythromycin will increase the level or effect of prednisone by affecting	6

		with increased effects of the drug	hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.	
DISPENSED MEDICINES IN THE PRIVATE SECTOR				
1. Ciprofloxacin/ Theophylline	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Ciprofloxacin will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP1A2 and CYP3A4 metabolism. Avoid or Use Alternate Drug. Concomitant use of theophylline and ciprofloxacin has decreased theophylline clearance and increased plasma levels and symptoms of toxicity.	4
2. Clarithromycin/ Loratadine	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Clarithromycin will increase the level or effect of loratadine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.	1
3. Clarithromycin /Prednisone	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Clarithromycin will increase the level or effect of prednisone by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.	5
4. Clarithromycin/ Theophylline	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Clarithromycin will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.	3
5. Doxycycline/ Amoxicillin	Private/Dispensing doctor	Antagonistic action	Doxycycline decreases effects of amoxicillin by pharmacodynamic antagonism. Avoid or Use Alternate Drug.	1
6. Erythromycin/ Theophylline	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Erythromycin will increase the level or effect of theophylline by affecting hepatic/intestinal enzyme CYP3A4 metabolism.	2

			Avoid or Use Alternate Drug.	
7. Prednisone/ Erythromycin	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Erythromycin base will increase the level or effect of prednisone by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Avoid or Use Alternate Drug.	1

3.5 Compliance with legislation by prescriptions

The compliance to legislation by a prescription was evaluated by assessing if the prescription provided by the non-dispensing private doctors had all the legal requirements as set out by Regulation 33, of the Medicines and Related Substances Control Act 101 of 1965 (Table 3.11). All the prescriptions in this study, i.e., 100% (n=181) had the prescriber's name, prescriber's address, prescriber's contact details, and approved name of each medicine (Table 3.11). However, only 13.8% (n=25) of the prescriptions had the patient's Identification number and patient's age (Table 3.11). Only 8.3% (n=15) of the prescriptions had the patient's address (Table 3.11). No prescription was fully compliant with the legislation or had all the legal requirements in this study (Table 3.11).

Table 3.11: Compliance with the legislation of a prescription

Prescribing parameter	**Category**	**Number of prescriptions (%)**
1.Date	C	179 (98.9%)
	NC	2 (1.1%)
2. Prescriber name	C	181 (100%)
	NC	0 (0%)
3.Prescriber address	C	181 (100%)
	NC	0 (0%)
4.Prescriber signature	C	180 (99.4%)
	NC	1 (0.6%)
5.Prescriber qualifications	C	172 (95.0%)
	NC	9 (5.0%)
6.Prescriber's MP Number	C	180 (99.4%)
	NC	1 (0.6%)
7.Prescriber contact details	C	181 (100%)
	NC	0 (0%)
8.Patient's Identification (ID)	C	25 (13.8%)

number	NC	156 (86.2%)
9.Patient's name	C	179 (98.9%)
	NC	2 (1.1%)
10.Patient's address	C	15 (8.3%)
	NC	166 (91.7%)
11.Patient's age	C	25 (13.8%)
	NC	156 (86.2%)
12.Patient's gender	C	84 (46.4%)
	NC	97 (53.6%)
13.Approved name of medicine/s	C	181 (100%)
	NC	0 (0%)
14.Dosage form/s	C	51 (28.2%)
	NC	130 (71.8%)
15.Strength	C	141 (77.9%)
	NC	40 (22.1%)
16.Quantity	C	125 (69.1%)
	NC	56 (30.9%)
17.Instructions of taking the medicine	C	180 (99.4%)
	NC	1 (0.6%)
*C – Compliant **NC – Non-compliant		

3.6 Compliance to legislation by dispensed medicines

For all the dispensed medicines, 40% (n=182) from the PHC nurses and 70% (n=559) from the private dispensing doctors had printed labels on the original containers (Table 3.12). These labels on original containers were compliant with Regulation 8 of the Medicines and Related Substances Control Act 101 of 1965, as amended (Table 3.12). The other dispensed medicines, i.e., 60% (n=272) in the public sector and 30% (n=239) in the private sector were repacked from bulk containers into smaller containers (Table 3.12). These labels for medicines that had undergone pre-packing were made in line with section 2.19 of the Good Pharmacy Practice (GPP) manual and Act 101 of 1965, as amended (Table 3.12).

Table 3.12: Distribution of labels for dispensed medicines

Category	**Primary Healthcare Nurse (Public Sector-Dispensed)**	**Dispensing doctor (Private Sector-Dispensed)**
Total number of drugs	454 (100%)	798 (100%)

Number of drugs with labels on original containers	182 (40%)	559 (70%)
Number of drugs that were repacked from bulk containers into smaller containers and with labels specific to repacking	272 (60%)	239 (30%)

All labels from the PHCs had the approved name of the medicine, however, only one label in the private sector had no approved name of the medicine (Table 3.13). All labels in the private sector had the directions of use, while 91.8% (n=167) of the labels in the public sector had directions of use (Table 3.13). No label in the public sector had the name of the dispenser or healthcare provider, while only 27.7% (n=155) of the labels in the private sector had the name of the dispenser (Table 3.13). Interestingly also, in both the private and public sectors, over 60% of the medicine packets did not have the patients' names. In the private sector, 3.4% (n=19) labels were fully compliant to the legislation of a dispensed medicine in line with regulation 8 of Act 101 of 1965, as amended (Table 3.13). In the public sector, no label was fully compliant with the legislation of a dispensed medicine in line with Regulation 8 of Act 101 of 1965, as amended (Table 3.13).

The research revealed that there were no statistically significant differences ($p > 0.05$) between private dispensing doctors and PHC nurses in the labelling of the name of the patient ($p = 0.199$) and the reference number ($p = 0.227$) (Table 3.13). The results show that there was a statistically significant difference between the compliance to legislation for labels on original containers of medicines, for the approved name of the medicine, directions of use, name of the dispenser, and business address of the dispenser, in the private sector, compared to the public sector ($p<0.001$) (Table 3.13).

Table 3.13: Compliance with legislation for labels on original containers

Labelling parameter	Category	PHC nurse (Public sector)	Dispensing doctor (Private sector)	*p*-Value
1.Date of dispensing	C	13 (7.1%)	30 (5.4%)	0.373
	NC	169 (92.9%)	529 (94.6%)	
2.Approved name of the medicine	C	182 (100%)	558 (99.8%)	< 0.001
	NC	0 (0%)	1 (0.2%)	
3.Name of patient	C	61 (33.5%)	217 (38.8%)	0.199
	NC	121 (66.5%)	342 (61.2%)	
4.Directions of use which may include: -Dose -Dosage intervals -Duration -Special instructions, e.g., finish the course for antibiotics	C	167 (91.8%)	559 (100%)	< 0.001
	NC	15 (8.2%)	0 (0%)	
5.Name of dispenser or healthcare provider	C	0 (0%)	155 (27.7%)	< 0.001
	NC	182 (100%)	404 (72.3%)	
6.Business address of the dispenser or healthcare provider	C	1 (0.5%)	149 (26.7%)	< 0.001
	NC	181 (99.5%)	410 (73.3%)	
7.Reference number	C	3 (1.6%)	19 (3.4%)	0.227
	NC	179 (98.4%)	540 (96.6%)	
*C – Compliant **NC – Non-compliant *p < 0.05 (significant).				

There was non-compliance to legislation for the business address at 99.3% in PHC and 73.3% in the private sector, respectively. Approximately 98% of the repackaged medicines in both sectors lacked an expiry date and a batch number. Of all the medicines repackaged,

only 2% in the private dispensing doctors and 0.7% in PHC fully complied with the labelling legislation of a dispensed repackaged medicine in line with section 2.19 of the GPP and Act 101 of 1965, as amended (Table 3.14). The study found that there were no statistically significant differences between dispensing doctors in the private sector and PHC nurses in the public sector in terms of labelling for the batch number ($p = 0.397$), reference number ($p = 0.397$), and expiry date ($p = 0.836$), (Table 3.14). (Table 3.13).

Both sectors were fully compliant with the legislation for the labelling parameter of the approved name of the medicine and there was a statistically significant difference ($p<0.001$) (Table 3.14). Dispensing doctors from the private sector labelled dispensed medicines with the directions of use, name of packaging institution and business address of the packaging institution more often than did the PHC nurses from the public sector ($p<0.001$) (Table 3.14).

Table 3.14: Compliance to legislation for medicines that have been repacked

Labelling parameter	**Category**	**PHC nurse (Public sector)**	**Dispensing doctor (Private sector)**	***p*-Value**
1.Packaging Date	C	20 (7.4%)	13 (5.4%)	0.379
	NC	252 (92.6%)	226 (94.6%)	
2.Approved name of the medicine	C	272 (100%)	239 (100%)	< 0.001
	NC	0 (0%)	0 (0%)	
3.Name of patient	C	92 (33.8%)	93 (38.9%)	0.232
	NC	180 (66.2%)	146 (61.1%)	
4.Directions of use which may include: -Dose -Dosage intervals -Duration -Special instructions, e.g., finish the course for antibiotics	C	249 (91.5%)	239 (100%)	< 0.001
	NC	23 (8.5%)	0 (0%)	
5.Name of packaging institution	C	2 (0.7%)	66 (27.6%)	< 0.001

	NC	270 (99.3%)	173 (72.4%)	
6.Business address of packaging institution	C	2 (0.7%)	64 (26.7%)	< 0.001
	NC	270 (99.3%)	175 (73.3%)	
7.Reference number	C	4 (1.5%)	6 (2.5%)	0.397
	NC	268 (98.5%)	233 (97.5%)	
8.Packaging Batch number	C	4 (1.5%)	6 (2.5%)	0.397
	NC	268 (98.5%)	233 (97.5%)	
9.Strength	C	92 (33.8%)	93 (38.9%)	0.232
	NC	180 (66.2%)	146 (61.1%)	
10.Quantity	C	91 (33.4%)	94 (39.3%)	0.167
	NC	181 (66.6%)	145 (60.7%)	
11.Expiry date	C	5 (1.8%)	5 (2.1%)	0.836
	NC	267 (98.2%)	234 (97.9%)	
12.Storage conditions and/or Warnings	C	150 (55.1%)	147 (61.5%)	0.146
	NC	122 (44.9%)	92 (38.5%)	
*C – Compliant **NC – Non-compliant *$p < 0.05$ (significant).				

3.7 Summary

This chapter outlined the results which were obtained from this study. The use of medicines that are not recommended by guidelines such as antibiotics, corticosteroids, and a major problem of polypharmacy was observed, especially with combination medicines. The public sector had a much lower percentage of drug-drug, interactions than the private sector. No prescription out of the total 181 prescriptions, was fully compliant with legislation. The dispensing doctors from the private sector were more compliant with the standard labelling requirements for dispensed medicines than the PHC nurses from the public sector. A hundred and eighty-one patient visits for prescriptions and 378 patient visits for dispensed medicines gave all the results which were presented in this chapter. The discussion for these results will be given in Chapter 4.

CHAPTER 4: DISCUSSION

4.1 Introduction

This chapter will give a detailed discussion of the results that were obtained from this study. This study aimed to assess prescribing patterns, dispensing practices, medicine utilization, and legal aspects in the treatment of acute bronchitis in both private, and public primary healthcare settings in Johannesburg.

4.2 Prescribing and dispensing patterns for acute bronchitis

Globally, primary healthcare settings are commonly known to provide therapies for the management of acute bronchitis (Albert, 2010; Porter and Kaplan, 2011; Little *et al.* 2013; Kinkade and Long, 2016; Smith *et al.*, 2017; Singh *et al*., 2019). In South Africa, primary health care can be provided by both the private and public sectors (National Department of Health, 2016). Public healthcare clinics are normally staffed by PHC nurses who diagnose, prescribe, and dispense medication, however, there are public PHCs that have doctors and pharmacists (National Department of Health, 2016).

In private healthcare, patients visit general practitioners or doctors who diagnose and prescribe medication (National Department of Health, 2017). If a doctor has a dispensing license, he or she can dispense medication (National Department of Health, 2017). Section 22C of the Medicines and Related Substances Control Act 101 of 1965, requires doctors to have a license for dispensing medication in practice (National Department of Health, 2017). The conditions for the granting of a dispensing license are given by regulation 18 to the Act (National Department of Health, 2017). The application for a dispensing license is received, reviewed, and approved by Director-General of the Department of Health (National Department of Health, 2017). Regulation 18 requires the application to contain at least the following information: name of the applicant, residential and business addresses of the applicant; location of the proposed dispensing premises, proof of qualification; telephone and fax numbers of the applicant; proof of registration with a statutory council; a copy of the required notice to other health facilities; motivation as to the need for a

dispensing license; and any additional information that the Director-General may require (National Department of Health, 2017).

As expected, the public sector had 100% compliance with generic medicines compared to the private sector which had a mix of generic and original medicines. The government sector policies such as the National Drug Policy mandates the use of generic medicines in their formularies (Essential Drugs List and Standard Treatment Guidelines) so as, to ensure access and affordability of medicines to all (Patel *et al*, 2012). The NDP implemented generic substitution in 2003 to further reduce spending (Gray *et al.*, 2016). The goal of this policy was to bring generic prescribing to both the private and public sectors (Gray *et al.*, 2016). The NDP was dedicated to the use of interchangeable multisource pharmaceutical products (IMPP) or generics, referred to by the international non-proprietary name (INN) or generic name (Gray *et al.*, 2016). Medicines on the National Essential Medicines List are mostly generic because substitution is not allowed in public sector facilities, since only those drugs bought through tender are available. (Gray *et al.*, 2016).

The tender process, which has been in place since 1982, is used to buy medicines in the public sector (Wouters *et al*., 2019). In essence, the procedure is the bulk purchase of drugs at a predetermined price for a set length of time after a competitive bidding process (Wouters *et al*., 2019). All interested parties are welcome to submit bids if they have marketing authorization from the national medicines' authority (Wouters *et al*., 2019). The government's tender quantities are based on previous year's usage patterns and epidemiological projections (Wouters *et al.*, 2019). The figures are not enshrined in law, and the government may propose lower or higher sums (Wouters *et al*., 2019). The bidding process is intended to increase competition among generic medicine manufacturers and lower drug prices (Wouters *et al*., 2019).

The private sector uses less generics than the public sector because they can afford more originator medicines (Gray *et al.*, 2016). Healthcare services in the private sector are primarily funded by medical aid schemes, with a small portion funded by out-of-pocket payments (Modisakeng *et al.*, 2020). Since the private sector is not governed by policies, the choices of medicines available to the private sector are wider compared to the public sector. The decision to prescribe an original or generic is left solely to the prescriber and

the dispenser, unlike the public sector that has a defined formulary to choose from. The picture thus is indifferent in the private sector with a combination of generic and original medicines.

In the private sector, 109 antibiotics were prescribed, while 152 antibiotics were dispensed and in the public sector, 141 antibiotics were dispensed. The use of antibiotics in the treatment of acute bronchitis is concerning particularly because many guidelines do not recommend the use of antibiotics for acute bronchitis (Woodhead *et al.*, 2011; American Academy of Pediatrics, 2015; Kinkade and Long, 2016; National Institute of Healthcare Excellence, 2016; National Department of Health, 2018).

Several studies have shown that antibiotics do not have any therapeutic benefits for acute bronchitis (Albert, 2010; Kinkade and Long, 2016). In addition, nine randomized clinical trials found that antibiotics produced insignificant benefits in symptom relief for acute bronchitis (Singh *et al.*, 2019). In the opinion of Togoobaatar *et al.* (2010), the effects of inappropriate antibiotic use are antimicrobial resistance, increased treatment costs, wastage of resources, adverse effects, and eroded patient confidence. It is very important to reduce and eventually stop the irrational use of antibiotics for acute bronchitis which will alleviate the concerns stated by Togoobaatar.

Healthcare professionals and the public should be educated on the dangers of irrational antibiotic use and how to reduce it. The most effective way to reduce antibiotic use for acute bronchitis is to establish antimicrobial stewardship policies in each primary care facility (Boyles *et al.*, 2013; Dodds Ashley *et al.*, 2014; National Department of Health, 2014; File *et al.*, 2014; Brinkmann and Kibuule, 2019; Engler *et al.*, 2020). Monitoring systems can be established to ensure that these policies are being adhered to (Brinkmann and Kibuule, 2019; Engler *et al.*, 2020). According to File *et al.* (2014), antimicrobial stewardship policies can minimize adverse effects, improve patient outcomes, decrease hospital stay, minimize financial costs, and curb antibiotic resistance. Further research needs to be done to investigate the factors that lead to irrational antibiotic use when treating acute bronchitis in primary care.

Oseltamivir was the only antiviral given in this study and yet several guidelines strongly

recommend the use of antivirals for acute bronchitis (Jefferson *et al.*, 2014; Singh *et al.*, 2019; Centre for Disease Control and Prevention, 2020; National Institute of Communicable Diseases, 2020). Antivirals are highly recommended for diseases such as acute bronchitis because they cure the disease by destroying the virus completely or by inhibiting its ability to replicate (Singh *et al.*, 2019; Centre for Disease Control and Prevention, 2020; National Institute of Communicable Diseases, 2020).

The use of corticosteroids in this study was concerning as there is inadequate evidence to support the utilization of corticosteroids for acute bronchitis (Albert, 2010; Becker *et al*., 2015; Singh *et al*., 2019). Corticosteroids are recommended for asthma and not for acute bronchitis (Albert, 2010; Becker *et al.*, 2015; Kinkade and Long, 2016; National Department of Health, 2018). Numerous studies discovered that corticosteroids show minimal benefits in relieving symptoms of acute bronchitis and have many adverse effects such as hyperglycemia and high blood pressure (Albert, 2010; Becker *et al*., 2015; Singh *et al.*, 2019).

Antihistamine use is seen as having a supportive role in the treatment of acute bronchitis and would be considered as appropriate treatment (Albert, 2010; Singh *et al.*, 2019), particularly in combination with decongestants to eliminate the cough (Kinkade and Long, 2016) Even though, antihistamines can cause adverse effects such as drowsiness and disturbed coordination (Kinkade and Long, 2016), they can be used in combination with other medicines to minimize adverse effects. Aniline analgesics given for acute bronchitis in this study were appropriate. Several studies recommend and support the use of aniline analgesics for acute bronchitis because they reduce both fevers as well as pain, with limited adverse effects (Albert, 2010; Little *et al*. 2013; Kinkade and Long, 2016; National Department of Health, 2018; Singh *et al.*, 2019).

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) were not appropriate to be given for acute bronchitis. Firstly, NSAIDs were unnecessary because acute bronchitis is not usually associated with pain (Albert, 2010; Kinkade and Long, 2016). A study that compared ibuprofen with a placebo showed that ibuprofen showed little benefit in reducing the severity or duration of cough in patients having acute bronchitis (Albert, 2010; Little *et al.*

2013; Kinkade and Long, 2016; Singh *et al*., 2019). Additionally, many adverse effects such as gastric ulcers, tinnitus, and kidney damage can be caused by NSAIDs (Albert, 2010; Little *et al.* 2013; Kinkade and Long, 2016; Singh *et al*., 2019

Nasal decongestants were appropriate for acute bronchitis in this study. However, nasal decongestants can cause rebound congestion or rhinitis medicamentosa if used alone and excessively (South African Medical Association, 2020). The use of nasal decongestants in combination with other medicines such as antihistamines is recommended because the risk of rebound congestion is reduced and there are more therapeutic benefits (Kinkade and Long, 2016; Smith *et al*., 2017; Singh *et al*., 2019).

Mucolytics were appropriate for acute bronchitis in this study. Several studies support the use of mucolytics in the management of acute bronchitis because they remove mucus easily which assists in alleviating the cough and they have very few adverse effects (Scaglione and Petrini, 2019). Since cough is the predominant sign of acute bronchitis, it is necessary to use an antitussive. Antitussives with pholcodine were given for acute bronchitis in this study. Antitussives with pholcodine are recommended and additionally, pholcodine has a good safety profile and does not cause addiction Findlay, 1988).

Very few xanthines were dispensed in the private sector, xanthines are indicated for the relief of bronchospasms caused by chronic obstructive pulmonary disease or asthma (South African Medical Association, 2020). Since acute bronchitis does not cause bronchospasms, xanthines were inappropriate to be given in this study. In addition, xanthines can cause adverse effects such as tachycardia and nervousness (South African Medical Association, 2020). Xanthines in combination with other medicines such as antihistamines are recommended for acute bronchitis because the potential for causing adverse effects is reduced (Albert, 2010; Kinkade and Long, 2016)

Twelve Leukotriene Receptor Antagonists (LRAs) mainly montelukast, were given for acute bronchitis in this study. Currently, there is no scientific evidence nor guideline that supports the use of LRAs for acute bronchitis. LRAs are recommended and beneficial in the chronic treatment of asthma (National Department of Health, 2018; South African Medical Association, 2020).

Short-Acting Beta Agonists (SABAs) mainly salbutamol was given, however, they are only recommended for acute bronchitis associated with wheezing and airflow obstruction (Becker *et al*., 2015; Kinkade and Long, 2016; Singh *et al*., 2019). Since wheezing nor airflow obstruction was not presented as symptoms by the standardized patients, the use of SABAs was not warranted. The Standard Treatment Guidelines (STGs) recommends the use of SABAs for asthma and not for acute bronchitis (National Department of Health, 2018; South African Medical Association, 2020). In addition, SABAs are associated with adverse effects such as tremors and nervousness (South African Medical Association, 2020).

Expectorants interestingly were not recommended to the standardized patients in this study considering that guaifenesin, is known to provide therapeutic benefits in the management of acute bronchitis (Kinkade and Long, 2016; Smith *et al*., 2017; Singh *et al*., 2019). Kinkade and Long (2016) reported that guaifenesin reduced the cough frequency and intensity by 75%.

A few complementary medicines (n=24) were given for this study. These are *hedera helix, echinacea purpurea, cinnamon,* a combination of *echinacea* and *sage leaves* as well as a combination of *gentian root, primula flower with calyx, common sorrel herb, elder flowers,* and *verbena*. *Hedera helix* or ivy leaf which had the highest frequency of 14, was appropriate to be given for acute bronchitis. Kruttschnitt *et al*. (2020) strongly support the use of *hedera helix* for acute bronchitis because it is safe and has many therapeutic benefits.

Echinacea purpurea (n=4) was appropriate to be given for acute bronchitis. Multiple randomized clinical trials have shown that *Echinacea purpurea* is safe and has many therapeutic benefits for acute bronchitis (Yale and Liu, 2004). *Cinnamon* (n=2) was appropriate to be used in the study because it has been used traditionally for centuries to treat acute bronchitis. Some authors highly recommend the use of *cinnamon* for acute bronchitis because it is safe and there is sufficient evidence to support its therapeutic benefits (Silver and Wilson, 2017). The other complementary medicines given such as Karvol® have insufficient evidence to support their effectiveness. Further research needs to be done to investigate their therapeutic benefits and safety in the treatment of acute bronchitis.

Vitamin C (n=14) was appropriate for acute bronchitis because it acts as an antioxidant (South African Medical Association, 2020). In a study involving 230 patients having acute bronchitis, vitamin C exhibited a significant improvement in symptom severity after administration (Evans *et al.*, 2002). For the other classes which were given such as multivitamins, combination drugs containing iron, and vitamin supplements, there is no sufficient evidence to support their therapeutic benefits for acute bronchitis. However, they are known to boost the immune system and their routine use can be recommended for immunocompromised patients with acute bronchitis and not in immunocompetent individuals. More studies should be done to evaluate their therapeutic benefits and pharmacovigilance aspects when used for acute bronchitis.

Certain medicines which are not indicated for acute bronchitis were given in this study such as the Angiotensin-converting enzyme inhibitor (ACEI) lisinopril, the Combined oral contraceptive (COC) Norgestrel/Ethinyl estradiol, the imidazole antifungals fluconazole and miconazole, the prokinetic agent metoclopramide and Proton Pump Inhibitors (PPIs) were prescribed. Misdiagnosis of the condition could have been a reason because the diagnosis was not consistent with the patient's signs and symptoms. The misdiagnoses are not many in this study, however, this relates to the inadequate knowledge and poor competence about identifying signs and symptoms of a condition (Velo and Minuz, 2009). Recommending the wrong drug can lead to untoward effects and be an expensive exercise as the patient will return with unresolved symptoms (Tully *et al*, 2009).

Combination medicines or fixed-dose combinations had the highest percentage, i.e., 29.0% (n=520) of the total 1789 drugs which were given for acute bronchitis in this study (Appendix O). Numerous studies have documented that combination medicines are highly beneficial for acute bronchitis because of the synergistic effects (Kinkade and Long, 2016; Smith *et al.*, 2017; Singh *et al.*, 2019). In addition, combination medicines have fewer adverse effects because the doses in combination medicines are usually low (Martinak *et al.*, 2017).

Moreover, many authors reported that the use of combination medicines helps to reduce problems such as addiction because of the low doses, for instance, combination medicines containing codeine (Albert, 2010; Woodhead *et al.*, 2011; Kinkade and Long, 2016).

However, many combination medicines containing codeine were prescribed and dispensed. Codeine can cause addiction and it is important to limit its use (South African Medical Association, 2020). Combination medicines containing dextromethorphan are very good alternatives for combination medicines containing codeine (Martinak *et al.*, 2017). This is because dextromethorphan does not potentiate addiction, it has more therapeutic benefits and has fewer adverse effects (Martinak *et al*., 2017). However, if very large doses of dextromethorphan are taken, it can cause some form of psychosis characterized by delusions, hallucinations, and paranoia (Martinak *et al*., 2017).

Polypharmacy is the concurrent use of multiple medicines by a single patient where they are not necessary nor indicated (World Health Organization, 2019). In this study, it was evident that the use of many drugs to treat a condition was higher in the private sector compared to the public sector. The limited formulary list in the public sector could be a contributing factor. Often doctors are pressured into prescribing unnecessarily as patients expect symptomatic treatment, which can contribute to polypharmacy (Albert, 2010). Polypharmacy is a growing public health problem in many clinical settings worldwide (World Health Organization, 2019) and can lead to non-adherence by patients (World Health Organization, 2019), cause drug-drug interactions, serious or life-threatening adverse effects (World Health Organization, 2019), wastage of resources and unnecessary financial costs (World Health Organization, 2019).

Primary healthcare settings can develop monitoring systems of dispensing and prescribing practices to prevent polypharmacy. Improving the knowledge of healthcare professionals by continuous professional development and access to current guidelines can increase best practices in the treatment of acute bronchitis. A medication management team can be established so that any polypharmacy cases are reported to them. Standard Operating Procedures should be made on how to handle polypharmacy cases in primary care. To prevent polypharmacy, regular audits should be done which assess how many medicines are given to patients (World Health Organization, 2020). More studies need to be done to investigate this problem of polypharmacy in primary care. The use of antibiotics for managing acute bronchitis has been discouraged and proven to be ineffective in many studies (Bent *et al.*, 1999; Knutson and Braun, 2002; Katende-Kyenda *et al.*, 2007; Ncube

et al., 2017; Smith *et al*., 2017). Even though there has been growing awareness of antibiotic resistance, the usage of antibiotics unnecessarily still exists. Acute bronchitis is mainly caused by viruses, however, up to two-thirds of patients in the United States are treated with antibiotics (Albert, 2010).

Monitoring systems should be put in place to ensure that treatment guidelines for acute bronchitis are adhered to (Kuper *et al*., 2019). Antimicrobial stewardship guidelines and reporting obligations are increasingly being placed on healthcare organizations (Kuper *et al*., 2019). This trend, combined with dwindling financial and human resources, has necessitated the use of Information Technology (IT) to alleviate these burdens and facilitate action (Kuper *et al*., 2019). Incorporating IT into an antimicrobial stewardship program can assist increase the efficiency of stewardship interventions and make tracking and reporting of critical indicators, such as outcomes, easier (Kuper *et al*., 2019).

A good example of a monitoring system is the bluebird health monitoring system which is used mainly in the private sector to reduce the risk of infections (Netcare Hospitals, 2016). Since the bluebird system was established recently, there are very few studies which have been done to assess its effectiveness in practice (Netcare Hospitals, 2016). For example, it was observed that the bluebird system caused an 18% reduction in antibiotic use by admitted patients of private hospitals and a subsequent decrease in unnecessary antibiotic use (Netcare Hospitals, 2016). Such a system can also be implemented in primary healthcare settings in order, to reduce the growing burden of antibiotic resistance (Netcare Hospitals, 2016). Adherence to treatment guidelines for acute bronchitis is important because this will ensure optimal patient care. Optimal patient care is the provision of safe and appropriate medicine to a patient responsibly, intending to achieve definite therapeutic outcomes that will improve the quality of life of the patient.

4.3 Drug-drug interactions

From the data sources, 29.34% (n=164) had drug-drug interactions. Most interactions were seen with diphenhydramine which belongs to the pharmacological class of antihistamines. Interestingly, medicines dispensed in the public sector had the lowest number of drug-drug interactions (n=27). This could be due to a limited formulary list of drugs in the primary

health care sector. Therefore, this limited formulary list with focused care could be the reason for the reduced drug-drug interactions. Additionally, the standard treatment guidelines (STGs) for acute bronchitis are clear and direct the prescriber to a simple and straightforward regimen (National Department of Health, 2018). In the private sector, the dispensed medicines had more interactions (n=341) than the prescribed medicines (n=129). This means that the non-dispensing doctors were more careful at minimizing drug-drug interactions than the dispensing doctors.

Some adverse effects of medicines for acute bronchitis are caused by drug-drug interactions (Albert, 2010; Kinkade and Long. 2016). A drug-drug interaction (DDI) is an activity that one drug has on another, resulting in a quantitative or qualitative alteration in the effects of both (Ziehl *et al*., 2019). Clinicians frequently administer many medicines at the same time in order, to achieve a greater therapeutic effect, which raises the risk of adverse drug effects (ADEs) due to DDIs (Ziehl *et al*., 2019). In healthcare settings, ADEs caused by DDIs are a critical challenge (Ziehl *et al*., 2019). The harmful effects of drug-drug interactions can be avoided by appropriately identifying important DDIs prior to therapy, considering pharmacological characteristics, delivery routes, and patient-specific variables (Ziehl *et al*., 2019). For health professionals, there are a variety of databases that provide information about drugs and their potential pharmacological interactions (Ziehl *et al*., 2019). Medscape®, Micromedex®, and Lexicomp® are the most regularly utilized databases, all of which use an algorithm to determine the prevalence and clinical significance of DDIs (Ziehl *et al*., 2019).

Most adverse effects which are caused by drug-drug interactions when treating acute bronchitis are due to Oral Inhaled Medicines (OIMs) (Ajimura *et al*., 2018). Common OIMs given for acute bronchitis include β_2 agonists, antimuscarinics, corticosteroids, antibiotics, mucolytics, antivirals, and combination products (Ajimura *et al*., 2018). Pharmacodynamic and pharmacokinetic interactions are two types of drug-drug interactions commonly found among medicines for respiratory diseases such as acute bronchitis (Ajimura *et al*., 2018). A pharmacodynamic interaction occurs when two or more drugs work together to produce additive, synergistic, potentiated, or antagonistic effects at the same or connected receptors (Ajimura *et al*., 2018). A pharmacokinetic drug

interaction occurs when a medication and/or its metabolite undergo changes in absorption, distribution, metabolism, and excretion (Ajimura *et al*., 2018). Pharmacokinetic drug interactions occur when one drug inhibits or induces the hepatic metabolism of another drug (Ajimura *et al*., 2018). For instance, when the inhaled corticosteroid (ICS) budesonide which is metabolized by the liver isoenzyme CYP P450 3A4, is given concurrently with a known inhibitor of CYP 3A4, such as the antifungal ketoconazole, a pharmacokinetic interaction occurs (Ajimura *et al*., 2018). Increased corticosteroid exposure is the result in this case, which might lead to adrenal suppression and/or weight gain (Ajimura *et al*., 2018).

The adverse effects caused by drug-drug interactions are unique such as changes in drug levels, increased risk of toxicity, additive anticholinergic effects, and corticosteroid accumulation with Cushing's syndrome (Ajimura *et al*., 2018). All prescribers should frequently examine and justify each patient's medication regimen, paying special attention to drug interactions (Ajimura *et al*., 2018). For the interpretation and management of possible medication interactions, pharmacists are a valuable resource (Ajimura *et al*., 2018). This is a multidimensional process that entails assisting with medication selection, assessing every prescription order for potential interactions, conveying potential drug interactions to other members of the multidisciplinary team, and assisting with adverse reaction monitoring (Ajimura *et al*., 2018).

Potentially the increased number of drug-drug interactions in the private sector could be due to polypharmacy. Polypharmacy is known to be a major cause of drug-drug, interactions worldwide (World Health Organization, 2019). Drug-drug interactions can lead to an increased risk of toxicity and adverse effects which can be life-threatening (South African Medical Association, 2020).

An adverse drug reaction (ADR) is defined as a response to a medicine that is harmful, unintended, and occurs at any dose (National Department of Health, 2017). This study shows that 4.43% (n=22) of the drug-drug interactions had an increased risk of toxicity. Furthermore, drug-drug interactions can lead to wastage of resources, unnecessary treatment costs of adverse effects, and a reduction in the therapeutic benefits or no

therapeutic benefits at all (South African Medical Association, 2020). Continuous education on the benefits of adverse drug reaction reporting and training to recognize ADRs can reduce costs and improve quality of life.

Although policies and protocols on pharmacovigilance and adverse drug reactions are accessible, enforcing the policy is critical to increasing the awareness of adverse drug reaction reporting.

4.4 Compliance to legislation by prescriptions

Compliance and heeding to the Act and regulations of the Act in the medical environment is paramount as it serves to protect the safety of the patient. Although legislation exists, non-compliance is a concern (Stewart, 2011). Regulation 33, of the Medicines and Related Substances Control Act 101 of 1965, as amended outlines the legal requirements for a prescription (South African Pharmacy Council, 2017). All the prescriptions from this study belonged to the private sector. Of the 181 prescriptions, none were fully compliant.

Non-compliance was mainly related to the identification number, patient address, and age, which is understandable as the legislation to include these aspects is fairly, recent. In August 2017, there were amendments to the Medicines and Related Substances Act 101 of 1965. These amendments although almost 4 years old, seem to be not fully implemented by prescribers. One prescription did not have directions of use which can inadvertently lead to toxicity or adverse effects. The lack of a date on two prescriptions makes them invalid scripts as the validity of the script cannot be authenticated. As per legislation, prescriptions cannot be dispensed if they are longer than 6 months old (Medicines and Related Substances Control Act 101, 1965).

It is very concerning that some prescribers do not comply to the legislation when issuing prescriptions. Very few studies have been done worldwide regarding the compliance to legislation prescriptions and in South Africa there is none. Additionally, there is no literature which describes the factors which may lead to non-compliance to legislation by prescribers in South Africa. However, it is anticipated that factors such as lack of education

or ignorance could be the leading causes of non-compliance to the legislation of prescriptions. Prescribers must be educated routinely on the legal aspects of prescriptions, and they should stay up to date with trends on this legislation. Consequently, studies on the legal aspects of prescriptions should be done in South Africa and beyond so that problems can be identified, and interventions can be sought.

4.5 Compliance to legislation by dispensed medicines

The National Department of Health (2017) declared that a label made for any dispensed medicine and put on the original container from the manufacturer must be per regulation 8 of the Medicines and Related Substances Act 101 of 1965, as amended. In addition, the labels for dispensed medicines that have undergone repacking or repackaging must be labelled under section 2.19 of the GPP. For labels on original containers of medicines, the study discovered that there were no statistically significant differences ($p > 0.05$) between dispensing doctors in the private sector and PHC nurses in the public sector regarding labelling for the name of patient ($p = 0.199$) and reference number ($p = 0.227$), where dispensing doctors complied better than the PHC nurses.

Moreover, there were statistically significant differences between the compliance to legislation for labels on original containers of medicines except for the approved name of the medicine, directions of use, name of the dispenser, and business address of the dispenser ($p<0.001$). Dispensing doctors from the private sector labelled dispensed medicines with the directions of use, name of the dispenser, and business address of the dispenser more often than did the PHC nurses from the public sector ($p<0.001$).

For labels of repacked medicines, the study found that there were no statistically significant differences ($p > 0.05$) between dispensing doctors in the private sector and PHC nurses in the public sector in terms of labelling for the batch number ($p = 0.397$), reference number ($p = 0.397$) and expiry date ($p = 0.836$), where dispensing doctors complied better than PHC nurses. In addition, there were statistically significant differences between the compliance to legislation for labels of repacked medicines except for the approved name of the medicine, directions of use, name of packaging institution, and business address of

the packaging institution ($p<0.001$). Dispensing doctors from the private sector labelled dispensed medicines with the directions of use, name of packaging institution, and business address of the packaging institution more often than did the PHC nurses from the public sector ($p<0.001$).

In the private sector, 3.4% (n=19) labels were fully compliant to the legislation of a dispensed medicine in line with regulation 8 of Act 101 of 1965, as amended. In the public sector, no label was fully compliant with the legislation of a dispensed medicine with a label on the original container and in line with Regulation 8 of Act 101 of 1965, as amended. In the private sector, 2.1% (n=5) of the labels were fully compliant with the legislation of a dispensed medicine that had undergone pre-packing and in line with section 2.19 of the GPP and Act 101 of 1965, as amended. In the public sector, 0.7% (n=2) of the labels were fully compliant with the legislation of a dispensed medicine in line with section 2.19 of the GPP and Act 101 of 1965, as amended.

These results are very concerning because every label for a dispensed medicine is expected to comply fully with the relevant legislation (National Department of Health, 2017). Labelling of medicines is an important factor that affects medication safety because if a patient does not understand the label, this may cause many problems such as medication errors. many labels lacked the patient's name which creates the risk of a wrong patient taking the drug thus compromising the quality of care. Some labels lacked directions of use. As per the Medicines Act, regulation 8, and section 2.19 of the good pharmacy practice guidelines, medicines must be labelled appropriately.

Antihistamines cause drowsiness as a major adverse effect (South African Medical Association, 2020). It is important to write on the label to take antihistamines at night so that the patient's activities during the day are not negatively affected by drowsiness (South African Medical Association, 2020). More than 75% of labels with antihistamines did not have the instruction; take at night. Systemic corticosteroids such as prednisone are best taken in the morning because this is when the body produces most of its corticosteroid hormones (South African Medical Association, 2020). In other words, corticosteroids are

taken in the morning to mimic the body's natural production of cortisol (South African Medical Association, 2020). Even though systemic corticosteroids were not appropriate for acute bronchitis, more than 85% of labels with systemic corticosteroids did not have the instruction; take in the morning.

Patients must be told to finish the course of antibiotics so that those antibiotics are fully effective (South African Medical Association, 2020). Even though antibiotics were inappropriate for acute bronchitis, more than 90% of labels with antibiotics did not have the instruction; finish the course. Non-compliance to legislation for a dispensed medicine can cause many problems. If a label has no dose, a patient can take the wrong dose leading to an overdose. An overdose can result in toxicity or life-threatening adverse effects. In addition, if a medicine does not have an expiry date, a patient can take an expired medicine unknowingly and experience adverse effects. If a label does not have a batch number, it would be difficult to trace the medicine when a recall is made. If a label has no dispensing date or packaging date, it can be difficult to trace when that medicine was dispensed.

From all the labels in this study, about 40% of them were handwritten, while the remaining 60% were computer-generated. More handwritten labels were from the public sector, while more computer-generated labels were from the private sector. Additionally, the private sector was more compliant with the labelling legislation than the public sector. This may be due to the lack of computerized systems in the public sector. A computer-generated label is better than a handwritten label because the computer-generated label is more clear, legible, and indelible than a handwritten label. Healthcare providers should be educated on the benefits of computer-generated labels so that healthcare settings can purchase these in order, to prevent errors. In addition, validation software can be used on computerized systems for generating labels to ensure that the labels will have all the legal requirements in place. Healthcare providers such as PHC nurses and dispensing doctors should be educated on good dispensing practices so that they can ensure optimal patient care. Monitoring systems should be established in primary healthcare settings to ensure compliance with legislation for a dispensed medicine.

4.6 Summary

This chapter gave a detailed discussion of all the research findings from this study. Irrational medicine use, including the overuse of medicines that are not recommended by guidelines such as antibiotics, drug-drug interactions, polypharmacy, and non-compliance to legislation were discussed. More studies need to be done to investigate the factors which cause these problems in primary care so that interventions can be sought. The next chapter is the conclusion.

CHAPTER 5: CONCLUSION

5.1 Introduction

This chapter will give the conclusion for this entire study. Besides, the study limitations and recommendations are given. Several studies have been done to investigate the prescribing and dispensing practices of acute bronchitis in primary healthcare settings all over the world (Goossens *et al.*, 2005; Gulliford, 2014; Shapiro, 2014; Ncube *et al.*, 2017). However, these studies did not assess certain aspects that were assessed by this study such as supportive therapies, adherence to treatment guidelines, drug-drug interactions, and compliance to legislation. The research findings from this study will contribute new knowledge which can improve the prescribing patterns, dispensing practices, medicine utilization, and legal aspects in the treatment of acute bronchitis in both private, and public primary healthcare settings in Johannesburg.

5.2 Conclusion

This study assessed prescribing, dispensing practices, medicine utilization, and legal aspects in the treatment of acute bronchitis in both public primary and private healthcare settings. Data sources included prescriptions and dispensed medicines which were obtained from 559 patient visits by standardized patients pretending to have acute bronchitis. The patient visits were made to 186 doctors in private primary care settings and 73 public clinics. There were 181 prescriptions from 181 patient visits and all the dispensed medicines came from a total of 378 patient visits. The total number of medicines both dispensed and prescribed for this study was 1789 with 454 drugs dispensed in the public sector, 537 drugs prescribed in the private sector, and 798 drugs dispensed in the private sector.

The research question for this study was, are prescribing practices, dispensing practices, medicine utilization, and legal aspects in the treatment of acute bronchitis in primary healthcare settings in Johannesburg rational and adherent to evidence-based clinical practice guidelines. The results from this study indicate that some of these practices in the

treatment of acute bronchitis in primary healthcare settings in Johannesburg are irrational and non-adherent to evidence-based clinical practice guidelines.

The research findings which contributed to answering the research question are explained in detail below. Firstly, a major problem of polypharmacy was observed, especially in the private sector. In the public sector, the maximum number of drugs was 4, while in the private sector the maximum number of drugs was 7. Combination medicines or fixed-dose combinations were prescribed or dispensed most frequently (29.0%; n=520), followed by antibiotics (22.5%; 402) and thirdly corticosteroids (12.6%; 226). More antibiotics were given in the private sector at 37.8% (n=152) for medicines dispensed and 27.1% (n=109) for prescriptions while fewer antibiotics were given in the public sector at 35.1% (n=141) for medicines dispensed. Medicines such as antibiotics and corticosteroids were frequently prescribed and dispensed, although many guidelines do not recommend the use of these medicines for acute bronchitis.

In 29.34% (n=164) of all the data sources, there was a total of 497 drug-drug interactions. More drug-drug, interactions were from the private sector at a frequency of 341 for medicines dispensed by dispensing doctors and 129 for prescribed medicines by non-dispensing doctors, while the public sector had the least interactions at a frequency of 27 for dispensed medicines by PHC nurses. This study revealed that some healthcare providers are not complying with the current legislation for labels of dispensed medicines and prescriptions. All the prescriptions from this study belonged to the private sector and no prescription out of the total 181 prescriptions, was fully compliant at 100% to the legislation of a prescription. For labels on original containers of medicines, the research revealed that there were no statistically significant differences ($p > 0.05$) between dispensing doctors in the private sector and PHC nurses in the public sector regarding labelling for the name of patient ($p = 0.199$) and reference number ($p = 0.227$), where dispensing doctors complied better than the PHC nurses.

Moreover, the differences between the compliance to legislation for labels on original containers of medicines were statistically significant except for the approved name of the medicine, directions of use, name of the dispenser, and business address of the dispenser ($p<0.001$). Dispensing doctors from the private sector labelled dispensed medicines with

the directions of use, name of dispenser, and business address of the dispenser more often than did the PHC nurses from the public sector ($p<0.001$).

For labels of repacked medicines, the research revealed that there were no statistically significant differences ($p > 0.05$) between dispensing doctors in the private sector and PHC nurses in the public sector regarding labelling for the batch number ($p = 0.397$), reference number ($p = 0.397$) and expiry date ($p = 0.836$), where dispensing doctors complied better than PHC nurses. Besides, there were statistically significant differences between the compliance to legislation for labels of repacked medicines except for the approved name of the medicine, directions of use, name of packaging institution, and business address of the packaging institution ($p<0.001$). Dispensing doctors from the private sector labelled dispensed medicines with the directions of use, name of packaging institution, and business address of the packaging institution more often than did the PHC nurses from the public sector ($p<0.001$).

In the private sector, 3.4% (n=19) labels were fully compliant to the legislation of a dispensed medicine in line with regulation 8 of Act 101 of 1965, as amended. In the public sector, no label was fully compliant with the legislation of a dispensed medicine with a label on the original container and in line with Regulation 8 of Act 101 of 1965, as amended. In the private sector, 2.1% (n=5) of the labels were fully compliant with the legislation of a dispensed medicine that had undergone pre-packing and in line with section 2.19 of the GPP and Act 101 of 1965, as amended. In the public sector, 0.7% (n=2) of the labels were fully compliant with the legislation of a dispensed medicine in line with section 2.19 of the GPP and Act 101 of 1965, as amended.

This study was very important because it gave a clear picture of the current prescribing and dispensing patterns for acute bronchitis in the primary healthcare settings of Johannesburg. Also, this study identified many problems in primary care that need immediate attention such as non-adherence to treatment guidelines, polypharmacy, drug-drug interactions, and non-compliance to legislation. Primary healthcare settings should develop monitoring systems of dispensing and prescribing practices to prevent non-adherence, polypharmacy, drug-drug interactions, and non-compliance to legislation. To reduce irrational antibiotic

use, antimicrobial stewardship policies should be implemented and adhered to in primary care.

Healthcare professionals should be educated about the dangers of non-adherence to guidelines through Continuing Professional Development (CPD) activities. Regular meetings and workshops can be done with healthcare providers in primary healthcare settings to educate them on rational dispensing and prescribing practices. In addition, more studies need to be done to investigate polypharmacy, drug-drug interaction, non-adherence, and non-compliance so that interventions can be established. To sum up, prescriptions and medicines dispensed should fully adhere to treatment guidelines because this will ensure optimal patient care. Optimal patient care is the provision of safe and appropriate medicine to a patient in a responsible manner, to achieve definite therapeutic outcomes that will improve the quality of life of the patient. In conclusion, Sir Mahatma Gandhi once said, "It is health that is real wealth and not pieces of gold and silver."

5.3 Study Limitations and Recommendations

Firstly, the prescriber's handwriting was difficult to see on some prescriptions and it was time-consuming to evaluate such prescriptions. Secondly, it was difficult to identify the brand of medicines that were packed in patient-ready packs or medicines which had been repacked, especially if the label did not have all the labelling parameters. In addition, this study was only done in primary healthcare settings in Johannesburg hence this prevented the generalization of the results to the whole country of South Africa.

Many recommendations were made after thoroughly assessing and discussing the research findings of this study. Firstly, healthcare providers in primary care should be educated on the dangers of irrational dispensing and prescribing practices through Continuing Professional Development (CPD) activities, conferences, regular meetings, and workshops. Posters and pamphlets can be used to educate healthcare providers in primary care about rational dispensing and prescribing practices. Secondly, the Standard Treatment Guidelines (STGs) for acute bronchitis in South Africa should be revised because they only mention symptomatic treatment and no curative treatment such as antivirals.

In addition, the scheduling statuses of codeine-containing combination medicines such as cough mixtures should be revised. Since codeine has a high risk of causing addiction, combination medicines or cough mixtures with high levels of codeine should not be sold over the counter but should be prescribed. Healthcare providers should be educated on opioid addiction and the need for strict measures when handling cough mixtures containing opioids. Additionally, healthcare professionals such as pharmacists can be employed as pharmacovigilance officers in each primary healthcare setting who will monitor and prevent adverse effects.

Moreover, the use of electronic dispensing systems and printed labels can be established in primary healthcare settings to improve compliance with the legislation for dispensed medicines. The use of printed prescriptions, except for the prescriber's signature can be established in primary healthcare settings to improve compliance with the legislation for prescriptions. To prevent polypharmacy, primary healthcare settings can develop monitoring systems of dispensing and prescribing practices. For example, a tracking system or regular audits can be made both physically and electronically to monitor the number of medicines given per patient. Computer software can be designed for primary care which allows the electronic prescribing of medicines, along with a prospective medicine audit with interventions and the delivery of feedback to prescribers. The feedback will educate the prescriber to ensure long-term rational prescribing.

Antimicrobial stewardship policies can be established in each primary care facility to reduce irrational antibiotic use. The public should be educated to refuse antibiotics from healthcare providers if they have confirmed acute bronchitis with no secondary bacterial infection using posters, social media platforms, and pamphlets. Social media platforms such as Twitter, Facebook, Linked-in, and Instagram can be used to educate the public about the dangers of irrational antibiotic use. Antigen test kits for common infections such as acute bronchitis should be put in every primary healthcare setting. This is important because the healthcare provider can confirm the cause of the disease before deciding on which medicines to give. Additionally, regular audits should be done in primary healthcare settings to investigate drug-drug interactions. Monitoring systems should be put in place to ensure the prevention of drug-drug interactions.

5.4 Recommendations for future studies

Many recommendations for future studies were made after analyzing the research findings of this study. Since this study was of a retrospective nature, a prospective study should be done as well to assess dispensing and prescribing patterns in primary care. Further research needs to be done on a larger population, for instance, a study should be done in primary healthcare settings in all provinces of South Africa to see the results for the whole of South Africa. Also, studies can be done to compare the costs of medicine used rationally and irrationally when treating acute bronchitis in primary healthcare settings.

There was no scientific evidence to support the use of some classes of medicines such as corticosteroids, complementary medicines, antiseptics, mouthwashes, and organochlorine compounds for acute bronchitis. As a result, more studies should be done to investigate the therapeutic benefits and safety profiles of these medicines in the management of acute bronchitis. Certain classes of medicines that are not indicated for acute bronchitis were given in this study which are Angiotensin-Converting Enzyme Inhibitors (ACEIs), Combined Oral Contraceptives (COCs), Proton Pump Inhibitors (PPIs), imidazole antifungals, and prokinetic agents. Further research needs to be done to assess factors that can cause such misdiagnoses in primary care and how to correct them.

Polypharmacy was found to be a major problem in this study. More studies need to be done to investigate the factors that lead to polypharmacy when managing acute bronchitis in primary healthcare settings. Moreover, studies need to be done to investigate factors that lead to non-adherence to evidence-based clinical practice guidelines in the treatment of acute bronchitis and non-compliance to the legislation of prescriptions and dispensed medicines.

5.5 Summary

The research findings of this study show that some of the dispensing and, prescribing practices for acute bronchitis in both private and public primary healthcare settings in Johannesburg are irrational and non-adherent to guidelines. Also, some healthcare

providers are not complying with the current laws for prescriptions and medicine labels. This is an area of great concern because there are many negative effects of non-adherence to guidelines and/or legislation such as wastage of resources, adverse effects, increased treatment costs, and poor patient outcomes. More studies need to be done to investigate the factors that lead to non-adherence when treating acute bronchitis so that problems can be identified, and solutions sought. Consequently, the implementation of strategies to improve adherence to evidence-based clinical practice guidelines and legislation is important so that there is optimal patient care.

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APPENDICES

APPENDIX A: Review article published from this study



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Abstract

Cough medicines are mostly given to patients presenting with a cough due to acute respiratory tract infections. Although cough is mainly a symptom of acute respiratory tract infections, it is also a symptom of many other diseases which are not of the respiratory system. A cough can be classified as acute if it lasts for 3 weeks or less, prolonged acute if it lasts between 3-8 weeks and chronic if it lasts for longer than 8 weeks. There are many cough medicines available on the market currently such as centrally acting agents, however, some of these medicines lack scientific evidence to support their therapeutic benefits and safety. There is ongoing research to investigate the safety aspects and therapeutic benefits of cough medicines in the management of respiratory diseases. Consequently, a pharmacist must make an informed healthcare decision before dispensing a cough medicine to a patient, taking into consideration its safety and therapeutic aspects. This review article offers insight into the types of cough medicines and their therapeutic applications. This article aims to give pharmacists the knowledge that can assist them in making an informed healthcare decision when dispensing a cough medicine to a patient so that they can ensure optimal patient care.

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APPENDIX B: The Therapeutic Applications of Cough Medicines in Respiratory Diseases

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Nelisa Paidamwoyo Ganga, The Therapeutic Applications of Cough Medicines in Respiratory Diseases

The Therapeutic Applications of Cough Medicines in Respiratory Diseases

Nelisa Paidamwoyo Ganga[1]

[1] *Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, Parktown Johannesburg 2193 Gauteng, South Africa.*

ABSTRACT

Cough medicines are mostly given to patients presenting with a cough due to acute respiratory tract infections. Although cough is mainly a symptom of acute respiratory tract infections, it is also a symptom of many other diseases which are not of the respiratory system. A cough can be classified as acute if it lasts for 3 weeks or less, prolonged acute if it lasts between 3-8 weeks and chronic if it lasts for longer than 8 weeks. There are many cough medicines available on the market currently such as centrally acting agents, however, some of these medicines lack scientific evidence to support their therapeutic benefits and safety. There is ongoing research to investigate the safety aspects and therapeutic benefits of cough medicines in the management of respiratory diseases. Consequently, a pharmacist must make an informed healthcare decision before dispensing a cough medicine to a patient, taking into consideration its safety and therapeutic aspects. This review article offers insight into the types of cough medicines and their therapeutic applications. This article aims to give pharmacists the knowledge that can assist them in making an informed healthcare decision when dispensing a cough medicine to a patient so that they can ensure optimal patient care.

Key Words: *Acute cough, Chronic cough, Dry cough, Wet cough, Cough medicine.*

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INTRODUCTION

A cough is one of the common symptoms for which patients seek medical care, especially in primary healthcare settings worldwide [1]. Although cough is mainly a symptom of acute respiratory tract infections, it is also a symptom of many other diseases which are not of the respiratory system [1]. A cough can be classified as acute if it lasts for 3 weeks or less, prolonged acute if it lasts between 3-8 weeks and chronic if it lasts for longer than 8 weeks [1, 2]. A cough is an airway defense mechanism that helps to clear the airway upon irritation or obstruction through a protective reflex action so that breathing can occur normally [1-3]. An acute cough is mostly caused by a viral infection and rarely caused by a bacterial infection [2, 3].

It can be very difficult to manage an acute cough following a self-limiting viral respiratory tract infection and such a cough can impair the patient's quality of life [2, 3]. Coughs are also classified either as productive or non-productive [3]. A productive cough, also known as wet cough, allows the ejection of sputum or secretions from the lower respiratory tract so that breathing can continue normally [3]. On the other hand, a non-productive or dry cough does not bring up any secretions or mucus hence it has no useful purpose [3]. A cough can be treated symptomatically by both non-pharmacological and pharmacological approaches [2]. Many healthcare professionals, including pharmacists, usually recommend Over-The-Counter (OTC) cough medicines as the first-line treatment for a cough [3-5]. Even though many patients report to benefit from cough medicines, there continues to be a debate among researchers on the therapeutic benefits and safety aspects of these medicines [3]. Many researchers report that cough medicines have a placebo effect that helps to reduce the severity of symptoms [3].

Management

An acute cough caused by a viral infection is mostly self-limiting hence it is often unnecessary to give medication [3]. Nonetheless, many patients have reported that they

Corresponding author: Nelisa Paidamwoyo Ganga
Address: Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, Parktown Johannesburg 2193 Gauteng, South Africa.
E-mail: ✉ nelisaganga @ gmail.com
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have benefited from cough medicines while having an acute cough caused by a viral infection [3, 6]. Since a cough can be a symptom of a serious medical condition such as pneumonia, it is important to refer the patient to a doctor for further diagnosis [6]. **Figure 1** below gives the circumstances in which a referral is necessary for a patient presenting with a cough [2, 3, 6].



Figure 1. Circumstances in which a referral is needed for a coughing patient [2, 3, 6].

Cough medicines are made from a combination of different active ingredients which belong to various pharmacological classes [2, 3, 7]. There are many pharmacological classes, including but not limited to, centrally acting agents, antihistamines, demulcents, bronchodilators, mucolytics and expectorants [2, 3, 7].

Antihistamines

Many antihistamines are found in cough medicines, although there is insufficient evidence to support their therapeutic benefits and safety for a cough [2]. Antihistamines are known to act either as antitussives or cough suppressants when alleviating a cough [2, 3]. First-generation antihistamines can antagonize acetylcholine at neuronal and neuromuscular muscarinic receptors, while second-generation antihistamines cannot [8]. Since second-generation antihistamines lack anticholinergic effects, they cannot alleviate a cough [9]. As a result, first-generation antihistamines are found in cough medicines and second-generation antihistamines are not [9]. Antihistamines act by decreasing the cholinergic transmission of nerve impulses in the coughing reflex thus suppressing the cough [10]. The sedative effect of first-generation antihistamines is highly beneficial for a cough that disturbs sleep [10]. Antihistamines are beneficial for a patient presenting with a cough, associated with a cold because apart from alleviating the cough, they also dry up the mucus or phlegm [10]. However, this drying effect of antihistamines can lead to problems such as the thickening of mucus or phlegm [11].

Centrally acting agents

Centrally acting agents are more effective for a chronic cough than for acute cough [2]. Centrally acting agents are considered unsafe for children under the age of 6 hence they should not be given to such patients [2]. Centrally acting agents, also known as, cough suppressants or antitussives act by decreasing the release of nerve impulses that cause coughing at the coughing centre in the brain [3]. It is not recommended to give codeine for the alleviation of cough because it has a very high risk of causing adverse effects [3]. Codeine, which is a centrally acting agent did not show any benefit in alleviating a cough for two studies that were done [12]. Three clinical trials showed that dextromethorphan decreased the cough count by 19% to 36% in comparison to a placebo [12]. Although dextromethorphan is preferred to codeine for alleviating a cough, it can cause serious toxicity if an incorrect dose is used [13]. A summary of the common centrally acting agents used for alleviating cough and their properties is given in **Table 1** below [2, 3, 12, 13].

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Table 1. Centrally acting agents [2, 3, 12, 13]

Example	Mechanism of Action	Adverse effects	Special Warnings
Codeine	Acts as a cough suppressant by suppressing the cough centre in the medulla	Constipation, Nausea and Sedation	Risk of drug addiction and abuse
Dextromethorphan	It is an N-Methyl D-aspartate (NMDA) receptor antagonist that acts directly by suppressing the medullary cough centre	Dizziness, Nausea, and Sedation	Risk of serious toxicity associated with excitation and confusion when an overdose is given
Pholcodine	Acts by directly suppressing the medullary centre	Constipation, Dizziness, Headache, Sedation, and Nausea	Risk of opioid dependence and abuse

Demulcents

Demulcents are also classified as cough suppressants or antitussives due to their voluntary suppression of cough [3, 6, 7]. Demulcents are usually recommended for infants under 2 years of age, children, and pregnant women because of their therapeutic benefits and safety profile [3, 6, 7]. Sucrose, honey, and alcohol are three examples of commonly used demulcents for alleviating a cough [11]. Demulcents act by coating the throat and soothing the irritated mucous membranes [11]. They also increase saliva production and swallowing thus inhibiting the cough reflex [11]. However, cough medicines containing up to 40% alcohol are not recommended for use by patients [11]. Additionally, it is not recommended to use demulcents containing sugar for diabetic patients because this may increase their glucose levels [11].

Expectorants

Expectorants, also known as mucoactive agents, act by stimulating respiratory tract secretions thus increasing respiratory fluid volumes and decreasing the viscosity of the mucous [10]. Common adverse effects of expectorants include dizziness, rash, and a headache [10]. Expectorants must be used with caution in patients with gastrointestinal ulcers [10]. Ipecacuanha is an expectorant of choice which belongs to the complementary medicines class and it is very effective for alleviating a cough [10]. Other expectorants include creosote, menthol, and squill, however, these expectorants usually exhibit minimal therapeutic benefits when used at low doses [10]. The dose of guaifenesin required in an adult to effectively alleviate a cough is usually between 100-200mg hence it is important to ensure that the dose is within this range before dispensing the cough medicine to a patient [10].

Guaifenesin is the expectorant of choice which is usually recommended for patients [12]. Guaifenesin was found to reduce cough frequency and intensity by 75%, while placebo had a decrease of 31% in a particular clinical trial [12]. Guaifenesin can act by stimulating the cholinergic pathway thus increasing the release of mucous from glands in the airways [14]. Although ammonium chloride, sodium citrate, and glyceryl guaiacolate are commonly used as expectorants, they were found to produce less therapeutic benefits when compared with a placebo in several clinical trials [15].

Mucolytics

Mucolytics act mainly by decreasing the viscosity of the mucous and they are also referred to as mucoactive agents [13]. Examples of commonly used mucolytics include carbocisteine, N-acetylcysteine and bromhexine [13]. Even though carbocisteine and bromhexine are routinely used as cough remedies, they still lack scientific evidence regarding their therapeutic benefits and safety profile to support their use [13, 16]. Carbocisteine also belongs to the pharmacological class of mucoregulators [16]. N-acetylcysteine was found to decrease cough frequency and intensity in children older than 2 years after six to seven days of therapy, in several clinical trials [16]. Carbocisteine acts by regulating the metabolism of mucous-producing cells thus decreasing the viscosity of mucous [16]. The common adverse effects of carbocisteine include a headache and diarrhea [16]. Carbocisteine should be used in caution for patients with asthma and peptic ulcers [16]. Carbocisteine was found to reduce the adherence of pathogens such as bacteria and viruses to ciliated epithelial cells in vitro [16]. Carbocisteine also has anti-inflammatory properties and it can reduce inflammation caused by infections in the airway passages through the production of cytokines [16]. N-acetylcysteine can also protect against free radical damage [16].

Mucokinetics

Mucokinetics are not recommended for acute coughing in non-asthmatic children [7]. Mucokinetics, also known as bronchodilators belong to the class of mucoactive agents [10]. Mucokinetics are subdivided into three categories which are β_2 agonists, muscarinic receptor antagonists, and xanthines [10]. Mucokinetics act by relaxing the smooth muscles in the airways, increasing the expiratory flow, and reducing the volume of mucous secreted thus alleviating the cough [10]. Orciprenaline and Terbutaline are the most used β_2 agonists [10]. The common adverse

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effects of β_2 agonists include tachycardia, tremors, and headaches [10]. As a result, β_2 agonists should be used with caution in patients having cardiac arrhythmias, ischaemic heart disease, and hyperthyroidism [10].

Theophylline is the most used xanthine for alleviating a cough [13, 17]. Theophylline has a very narrow therapeutic window meaning that serious toxicity or lack of efficacy can occur if doses fall outside of the therapeutic range [13, 17]. Monitoring of theophylline levels in the blood can be done as a way to prevent or identify toxic effects [13]. Theophylline should be used with caution especially in children and the elderly who have a greater risk of experiencing the toxic effects of theophylline [13, 17]. Since there is an increased risk of toxicity, OTC medicines containing theophylline should not be taken at the same time as prescribed theophylline by an asthmatic patient [17].

Combination medicines

Many combination medicines are used for managing cough and they consist of various active ingredients belonging to different pharmacological classes [2, 3]. The goal of combination medicines is to allow synergistic mechanisms which will provide enhanced therapeutic benefits [2, 3]. Theophylline and orciprenaline are found in most combination medicines because when used in combination, their bronchodilatory effects are enhanced significantly [3, 6]. The combination of an antihistamine and an expectorant is not recommended for cough because these two classes have conflicting effects, while an antihistamine suppresses a cough, an expectorant promotes coughing [3, 7]. The combination of an antihistamine and a centrally acting agent is usually recommended for a cough that is disturbing one's sleep because these two classes both act as cough suppressants, both cause sedation, and can be given at night [3, 7]. Combination medicines containing bronchodilators, expectorants, and nasal decongestants are recommended for use in patients experiencing a productive cough, nasal congestion, and wheezing simultaneously [7]. Nasal decongestants such as phenylephrine and pseudoephedrine are commonly used in combination medicines for alleviating a cough because they help in relieving nasal congestion [7].

A combination medicine containing a first-generation antihistamine and a nasal decongestant was found to relieve an acute cough and nasal congestion more effectively than a placebo, in one clinical trial [9]. One randomized clinical trial showed that naproxen, which is a Non-Steroidal Anti-inflammatory Drug (NSAID) was very effective in alleviating a cough hence this medicine can be investigated further before using it in practice [9]. Combination medicines for a cough containing antimuscarinic agents should be carefully considered before giving the patient because they are prone to suppress bronchial secretions and cause changes in the surface tension [18]. It is not recommended to use a combination medicine containing an expectorant and a centrally acting agent because a patient may fail to get any therapeutic benefit since these two pharmacological classes have contradictory effects [19].

Recommendations in practice

The choice of therapy is largely dependent upon the type of cough hence this should be taken into consideration before dispensing any medication [6, 7]. The pharmacist should ask the patient about the medication he or she is currently taking in order, to assess for any possible drug-to-drug interactions [7]. Cough suppressants containing dextromethorphan and pholcodine are usually recommended for a dry cough [7]. On the other hand, expectorants such as guaifenesin are mostly recommended for a wet cough [7]. Cough suppressants are also preferred when the cause of the cough is unknown and when the cough disturbs sleep [7]. However, cough suppressants are not recommended for a wet cough because they can cause the retention of mucus or phlegm in the lower respiratory tract thus increasing the risk of infection [7]. While cough suppressants reduce coughing, expectorants promote coughing hence it is not recommended to use these two medicines concomitantly [7]. It is highly recommended to use a full dose of one medicine when treating a cough that focuses on a specific part of the reflex [11]. The use of cough medicines particularly in infants and children needs to be carefully considered because such age groups are at a high risk of experiencing adverse effects of these medicines [20]. Demulcents are recommended for children younger than 2 years and pregnant women because they have fewer adverse effects [20]. Promethazine containing antihistamines are contraindicated for use in children under 2 years because of the risk of adverse effects [21].

CONCLUSION

The pharmacist must take into consideration the safety aspects, age, concurrent medication, and pre-existing conditions before dispensing a cough remedy to a patient because this will assist the pharmacist in making an informed healthcare decision. The pharmacist needs to give individualized therapy because each patient has his or her own specific healthcare needs. Further studies need to be done on the therapeutic and safety aspects of cough medicines which lack scientific evidence to support their use. Since drug abuse and addiction such as opioid abuse is on the rise worldwide, the pharmacist needs to assess patients requesting cough remedies for any signs of drug abuse and addiction. Every pharmacist must practice the

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responsible provision of cough medicines to achieve definite therapeutic outcomes that improve the patient's quality of life.

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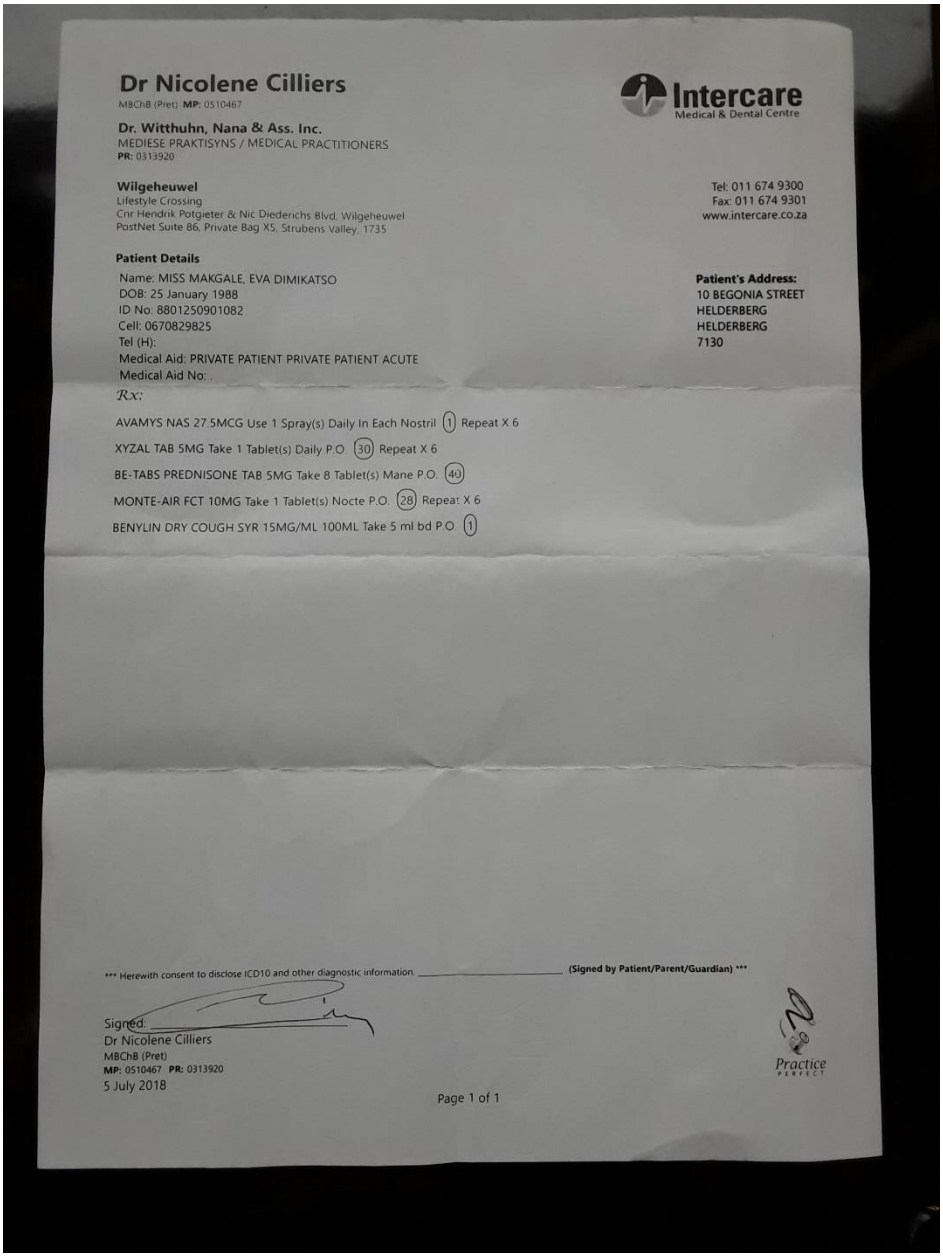
APPENDIX C: Example of a prescription used in this study



Dr Nicolene Cilliers
MBChB (Pret) **MP:** 0510467

Dr. Witthuhn, Nana & Ass. Inc.
MEDIESE PRAKTISYNS / MEDICAL PRACTITIONERS
PR: 0313920

Wilgeheuwel
Lifestyle Crossing
Cnr Hendrik Potgieter & Nic Diederichs Blvd, Wilgeheuwel
PostNet Suite 86, Private Bag X5, Strubens Valley, 1735

Intercare
Medical & Dental Centre

Tel: 011 674 9300
Fax: 011 674 9301
www.intercare.co.za

Patient Details
Name: MISS MAKGALE, EVA DIMIKATSO
DOB: 25 January 1988
ID No: 8801250901082
Cell: 0670829825
Tel (H):
Medical Aid: PRIVATE PATIENT PRIVATE PATIENT ACUTE
Medical Aid No: .

Patient's Address:
10 BEGONIA STREET
HELDERBERG
HELDERBERG
7130

Rx:

AVAMYS NAS 27.5MCG Use 1 Spray(s) Daily In Each Nostril (1) Repeat X 6

XYZAL TAB 5MG Take 1 Tablet(s) Daily P.O. (30) Repeat X 6

BE-TABS PREDNISONE TAB 5MG Take 8 Tablet(s) Mane P.O. (40)

MONTE-AIR FCT 10MG Take 1 Tablet(s) Nocte P.O. (28) Repeat X 6

BENYLIN DRY COUGH SYR 15MG/ML 100ML Take 5 ml bd P.O (1)

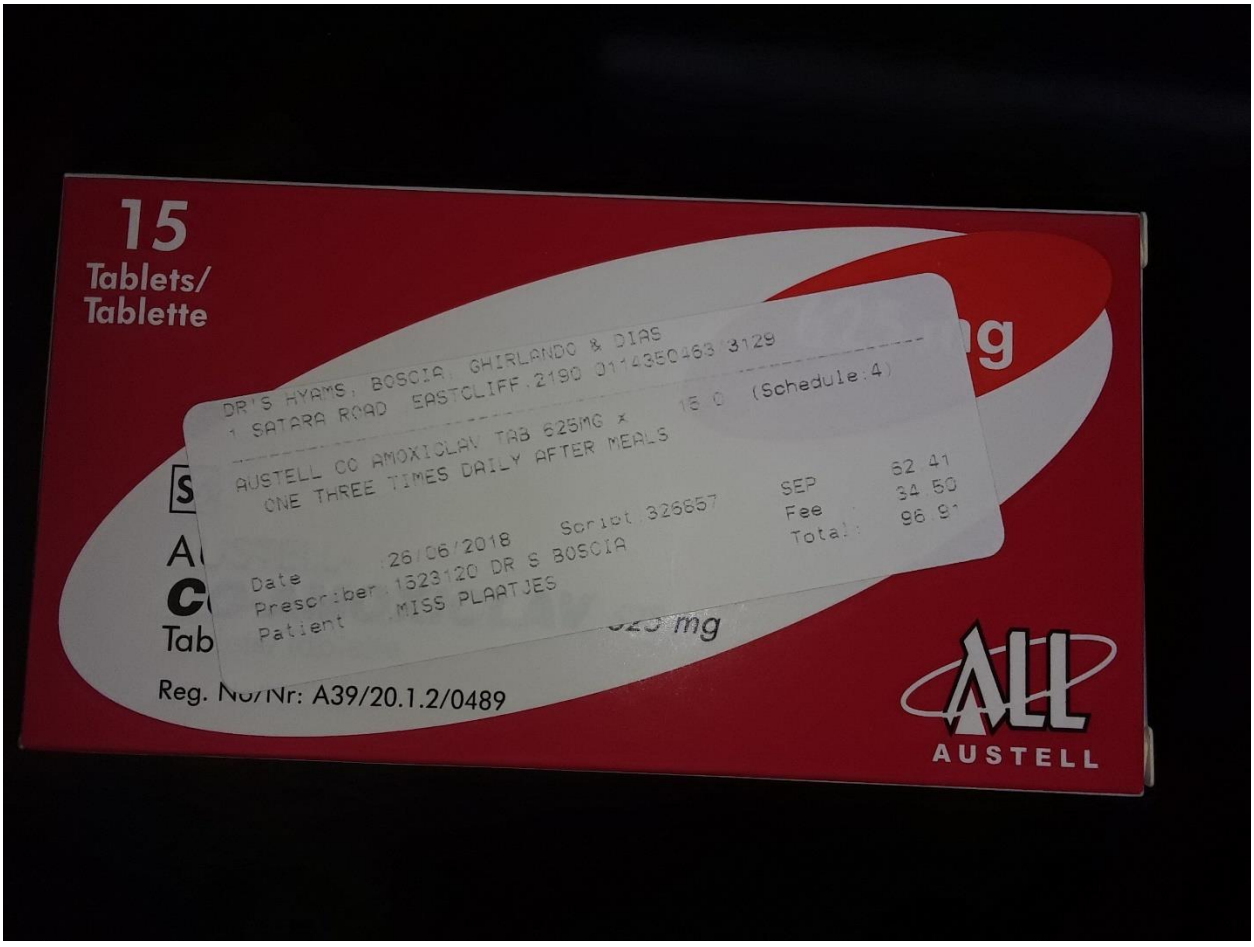
*** Herewith consent to disclose ICD10 and other diagnostic information. _____ **(Signed by Patient/Parent/Guardian)** ***

Signed: _____
Dr Nicolene Cilliers
MBChB (Pret)
MP: 0510467 **PR:** 0313920
5 July 2018

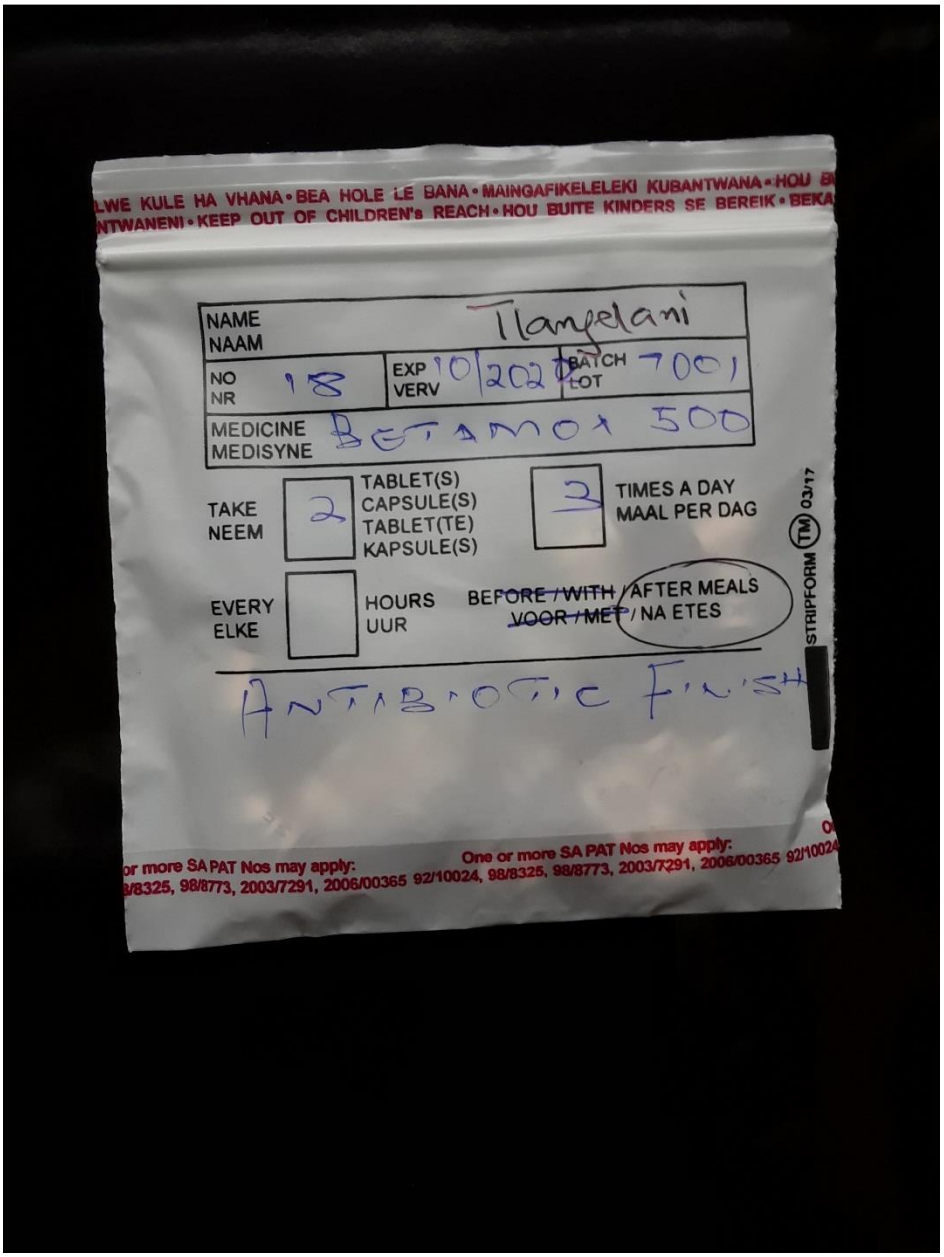
Practice PERFECT

Page 1 of 1

APPENDIX D1: Example of a label on the original container of a dispensed medicine



APPENDIX D2: Example of a label for a dispensed medicine which has undergone pre-packing



APPENDIX E: Summary of the previous study







DETERMINANTS OF ANTIBIOTIC PRESCRIBING IN PRIMARY CARE IN SOUTH AFRICA: STUDYING PATIENT-PROVIDER INTERACTIONS IN THE PRIVATE AND PUBLIC SECTORS

Mylene Lagarde[1], Duane Blaauw[2], Lenore Manderson[2]
[1]London School of Economics and Political Science, [2]University of the Witwatersrand

Summary

Because it increases the morbidity and mortality of bacterial infection, as well as the duration and cost of antibacterial treatment, antibiotic resistance constitutes a significant threat to global public health. The problem is even more critical in low- and middle-income countries which have higher infectious disease burdens, often higher rates of antibiotic resistance, less access to diagnostic tools, and fewer financial resources to purchase newer more effective antibiotics. In South Africa, antibiotic resistance is particularly high, despite an effective drug regulatory system and various initiatives to tackle the problem. Antibiotic resistance is accelerated by the overuse and over-prescription of antibiotics, which is the product of complex interactions between providers' decisions and knowledge, and patients' expectations. Yet research on the determinants of prescribing behaviours from LMICs in general, and South Africa in particular, is limited, and has been criticised for being too descriptive and superficial, with limited insight into the relative importance of different behavioural determinants to be able to prioritise interventions. In South Africa, most research efforts have focused on hospitals rather than primary care, despite the fact the majority of antibiotics are prescribed in primary care, mostly for respiratory infections.

This study aims to explore how the interactions between providers and patients influence inappropriate antibiotic prescribing for URTIs in public and private primary care in South Africa.

The study will include three components. First, drawing on medical anthropology, we will explore qualitatively providers' and patients' perceptions and experiences of antibiotic prescribing. This will be done through observations of consultations, interviews with providers and focus group discussions with patients. Second, building on the first part and drawing on methods from marketing research, we will design a survey consisting of a series of hypothetical clinical cases where clinical and patient characteristics will be systematically varied; for each case, the providers taking part will be asked indicate what drugs they would prescribe in a list of proposed drugs. The results will allow us to quantify the relative importance of the factors influencing antibiotic prescribing, with a view to inform policy-makers design future interventions. Finally, drawing on recent economics and medical education research, we will move beyond observational research and design a small randomised field study to test the impact of patients' knowledge and financial incentives on the prescribing practices of public and private primary care providers. This will be achieved with the use of standardised patients, who are healthy subjects trained to portray specific symptoms and disclose a rehearsed medical history. These patients will be sent to visit providers who agreed to take part in the research, at a time and under an identity unknown to them. The standardised patients will only differ in their expectations of antibiotics and the insurance status they will disclose. This will allow us to test the impact of these different characteristics on the likelihood of antibiotic prescription.

We anticipate that the results will provide invaluable insights into our understanding of prescribing decisions in the public and private sector in South Africa, thereby informing the stewardship programmes for antimicrobial resistance in this country. Beyond this setting, these findings will be useful to other middle-income countries with a similar mix of public and private providers. More generally, we aim to produce high-quality research and develop innovative methods that could be replicated in other low-income settings to study antibiotic prescribing.

APPENDIX F: Johannesburg Health District permission letter

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

Joburg
world class African city

JOHANNESBURG HEALTH DISTRICT

Enquiries: Dr EM Ohaja
Tel: +27(0) 11 694 3857
Cell: 062 731 6672 / 076 8831659
Email: Elizabeth.Ohaju@gauteng.gov.za
Hillbrow CHC: Administration Building
Cr Smith Str. & Kleu Street
Private Bag X21 Johannesburg
South Africa, 2017

67 19th Street
Parkhurst
Johannesburg

Duane.blaauw@wits.ac.za

Ref: 2017-05-006

NHRD Ref: GP_2017RP39_370

Dear. Dr Duane Blaauw

Re: *Determinats of antibiotic prescribing in primary care in South Africa: Studying patient-provider interactions in the private and public sectors*

Your application dated **2017/05/24** refers.

The District Research Committee has reviewed your application. This letter serves as an in-principle approval to access the Districts Health facilities (mentioned below) for the above project subject to following conditions:

The facility to be visited: Alex CHC, Mofolo CHC, Crosby Clinic, Parkhurst Clinic, Riverlea Clinic, Bellavista Clinic

The research can only commence after you submit an ethics clearance certificate from a recognized institution.

- The research can only commence after you submit an ethics clearance certificate from a recognized institution.
- This facility will be visited from 30/05/2017 to 30/05/2018
- You will report to the Facility Manager before initiating the study

Region	Regional Health Manager	Contact No.	Cell phone
AF	Ms Matlala	011 440 1259	082 307 0267
B	Ms Paulinah Maepa	011 718 9656	082 551 5804

- You will report to the Facility Manager before initiating the study.
- Participants' rights and confidentiality will be maintained all the time.
- No resources (Financial, material and human resources) from the above facilities will be used for the study. Neither the District nor the facility will incur any additional cost for this study.

- The study will comply with Publicly Financed Research and Development Act, 2008 (Act 51 of 2008) and its related Regulations.
- You will submit a copy (electronic and hard copy) of your final report. In addition, you will submit a six-monthly progress report to the District Research Committee.
- Your supervisor and University of South Africa will ensure that these reports are being submitted timeously to the District Research Committee.
- The District must be acknowledged in all the reports/publications generated from the research and a copy of these reports/publications must be submitted to the District Research Committee.

We reserve our right to withdraw our approval, if you breach any of the conditions mentioned above.

Please feel free to contact us, if you have any further queries. On behalf of the District Research Committee, we would like to thank you for choosing our District to conduct such an important study.

Regards,

Ms M Morewane
Chief Director
Johannesburg Health District
Date: 06/06/2017

APPENDIX G: Ethical clearance certificate for previous study

R14/49 Dr Duane Blaauw et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1611120

NAME: (Principal Investigator)	Dr Duane Blaauw et al
DEPARTMENT:	Centre for Health Policy School of Public Health Regions B and F, City of Johannesburg, Gauteng
PROJECT TITLE:	Determinants of Antibiotic Prescribing in Primary Care in South Africa: Studying Patient-Provider Interactions in the Private and Public Sectors
DATE CONSIDERED:	25/11/2016
DECISION:	Approved
CONDITIONS:	The Investigator has the responsibility to obtain permissions from the relevant research sites before any data may be collected
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

06/02/2017
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX H: London School of Economics approval letter for previous study

THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Houghton Street
London WC2A 2AE
United Kingdom

tel: +44 (0)20 7106 1202
email: rescon@lse.ac.uk
www.lse.ac.uk

Research Division

Dr Mylene Lagarde
Department of Social Policy
m.lagarde@lse.ac.uk

11th May 2017

Dear Dr Lagarde

Re: 'Determinants of antibiotic prescribing in primary care in South Africa: studying patient-provider interactions in the private and public sectors' [ref. 00513]

Further to my letter of 29th March giving ethical approval for Parts 1 and 2 of the above research project, and in light of the recent change in the informed consent procedures, I am now writing in my capacity as Chair of the Committee to give ethical approval for Part 3 and hence for the whole project.

Please note that any significant changes to the research design must be reported to the Research Ethics Committee. Amendments to the research design that may affect participants and/or that may have ethical implications must be reviewed and approved by the Research Ethics Committee before commencement (or recommencement) of the project. The Research Ethics Committee may periodically conduct a selective audit of current research projects.

I would like to take this opportunity to wish you well with your research project.
If you have any further queries, please feel free to contact Lyn Grove, Research Division.

Yours sincerely,

Professor John Worrall
Chair of the Research Ethics Committee

cc. Lyn Grove, Research Division

The London School of Economics is a School of the University of London. It is a charity and is incorporated in England as a company limited by guarantee under the Companies Acts (Reg. No 70527)

APPENDIX I: Permission letter for me to use the original data sources from the previous study

The Centre for Health Policy

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

3 November 2019

Ms Nelisa Ganga
Department of Pharmacy
University of the Witwatersrand

Dear Ms Ganga

Permission to use AMR study data

This letter is to confirm that I have agreed that you can use the data from our previous study for your Masters research project.

Our study was entitled "*Determinants of antibiotic prescribing in primary care in South Africa*" with Wits HREC clearance M1611120. The available study data that you will need for your study is in the form of:

- a Stata database of the data we have previously entered from the study visits,
- the physical scripts and drugs obtained at each visit.

Yours sincerely

Dr Duane Blaauw
Principal Investigator
Centre for Health Policy

Health Policy and Systems Research

3rd Floor, New School of Public Health Building, Wits Education Campus, 27 St Andrews Rd Parktown
Private Bag X3 Wits 2050 · Tel: 27 (0) 11 717 3420 · Fax: +27 (0) 86 568 9144 · www.wits.ac.za/chp

APPENDIX J: Ethical clearance certificate for this study

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Nelisa Ganga and Mrs Deanne Johnston

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M191085

NAME: (Principal Investigator)	Miss Nelisa Ganga and Mrs Deanne Johnston
DEPARTMENT:	Pharmacy and Pharmacology
PROJECT TITLE:	A medicine utilization study for viral bronchitis in primary healthcare setting in Johannesburg
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-Study
SUPERVISOR:	Mrs Neelaveni Padayache
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/11/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

08/11/2019
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX K: Protocol approval letter for this study

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

18 November 2019
Person No: 2307434
PAG

Miss NP Ganga
163 Odendaal Avenue
P.O. Box 211
Chipinge
Zimbabwe
+263
Zimbabwe

Dear Miss Nelisa Ganga

Master of Pharmacy: Approval of Title

We have pleasure in advising that your proposal entitled *A medicine utilization study of viral bronchitis in primary healthcare settings in Johannesburg* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX L: Uploaded Entered Data Tool

Uploaded Entered Data

vid	_____
number of drugs	_____
any ABs	◯ No ◯ Yes
number of ABs	_____
Sector	_____
Group	_____
drug1 script	◯ Dispensed ◯ Prescribed
drug1 name	_____
drug1 nappi	_____
drug1 active	_____
drug1 strength	_____
drug1 unit	_____
drug1 format	_____
drug1 form	_____
drug1 pack	_____
drug1 schedule	_____
drug1 quantity	_____

drug 1 atc	
drug 1 1st active ingredient	
drug1 strength 1st active ingredient	
drug1 unit 1st active ingredient	
drug1 2nd active ingredient	
drug1 strength 2nd active ingredient	
drug1 unit 2nd active ingredient	
drug1 3rd active ingredient	
drug1 strength 3rd active ingredient	
drug1 unit 3rd active ingredient	
drug1 4th active ingredient	
drug1 strength 4th active ingredient	
drug1 unit 4th active ingredient	
drug1 5th active ingredient	
drug1 strength 5th active ingredient	
drug1 unit 5th active ingredient	
drug2 script	◯ Dispensed ◯ Prescribed
drug2 name	

drug2 nappi	
drug2 active	
drug2 strength	
drug2 unit	
drug2 format	
drug2 form	
drug2 pack	
drug2 schedule	
drug2 quantity	
drug2 atc	
drug2 1st active ingredient	
drug2 strength 1st active ingredient	
drug2 unit 1st active ingredient	
drug2 2nd active ingredient	
drug2 strength 2nd active ingredient	
drug2 unit 2nd active ingredient	
drug2 3rd active ingredient	
drug2 strength 3rd active ingredient	

drug2 unit 3rd active ingredient	
drug2 4th active ingredient	
drug2 strength 4th active ingredient	
drug2 unit 4th active ingredient	
drug2 5th active ingredient	
drug2 strength 5th active ingredient	
drug2 unit 5th active ingredient	
drug3 script	◯ Dispensed ◯ Prescribed
drug3 name	
drug3 nappi	
drug3 active	
drug3 strength	
drug3 unit	
drug3 format	
drug3 form	
drug3 pack	
drug3 schedule	
drug3 quantity	

drug3 atc	
drug3 1st active ingredient	
drug3 strength 1st active ingredient	
drug3 unit 1st active ingredient	
drug3 2nd active ingredient	
drug3 strength 2nd active ingredient	
drug3 unit 2nd active ingredient	
drug3 3rd active ingredient	
drug3 strength 3rd active ingredient	
drug3 unit 3rd active ingredient	
drug3 4th active ingredient	
drug3 strength 4th active ingredient	
drug3 unit 4th active ingredient	
drug3 5th active ingredient	
drug3 strength 5th active ingredient	
drug3 unit 5th active ingredient	
drug4 script	◯ Dispensed ◯ Prescribed
drug4 name	

drug4 nappi	
drug4 active	
drug4 strength	
drug4 unit	
drug4 format	
drug4 form	
drug4 pack	
drug4 schedule	
drug4 quantity	
drug4 atc	
drug4 1st active ingredient	
drug4 strength 1st active ingredient	
drug4 unit 1st active ingredient	
drug4 2nd active ingredient	
drug4 strength 2nd active ingredient	
drug4 unit 2nd active ingredient	
drug4 3rd active ingredient	
drug4 strength 3rd active ingredient	

drug4 unit 3rd active ingredient	
drug4 4th active ingredient	
drug4 strength 4th active ingredient	
drug4 unit 4th active ingredient	
drug4 5th active ingredient	
drug4 strength 5th active ingredient	
drug4 unit 5th active ingredient	
drug5 script	◯ Dispensed ◯ Prescribed
drug5 name	
drug5 nappi	
drug5 active	
drug5 strength	
drug5 unit	
drug5 format	
drug5 form	
drug5 pack	
drug5 schedule	
drug5 quantity	

drug5 atc	
drug5 1st active ingredient	
drug5 strength 1st active ingredient	
drug5 unit 1st active ingredient	
drug5 2nd active ingredient	
drug5 strength 2nd active ingredient	
drug5 unit 2nd active ingredient	
drug5 3rd active ingredient	
drug5 strength 3rd active ingredient	
drug5 unit 3rd active ingredient	
drug5 4th active ingredient	
drug5 strength 4th active ingredient	
drug5 unit 4th active ingredient	
drug5 5th active ingredient	
drug5 strength 5th active ingredient	
drug5 unit 5th active ingredient	
drug6 script	◯ Dispensed ◯ Prescribed
drug6 name	

drug6 nappi	
drug6 active	
drug6 strength	
drug6 unit	
drug6 format	
drug6 form	
drug6 pack	
drug6 schedule	
drug6 quantity	
drug6 atc	
drug6 1st active ingredient	
drug6 strength 1st active ingredient	
drug6 unit 1st active ingredient	
drug6 2nd active ingredient	
drug6 strength 2nd active ingredient	
drug6 unit 2nd active ingredient	
drug6 3rd active ingredient	
drug6 strength 3rd active ingredient	

drug6 unit 3rd active ingredient	
drug6 4th active ingredient	
drug6 strength 4th active ingredient	
drug6 unit 4th active ingredient	
drug6 5th active ingredient	
drug6 strength 5th active ingredient	
drug6 unit 5th active ingredient	
drug7 script	◯ Dispensed ◯ Prescribed
drug7 name	
drug7 nappi	
drug7 active	
drug7 strength	
drug7 unit	
drug7 format	
drug7 form	
drug7 pack	
drug7 schedule	
drug7 quantity	

drug7 atc	
drug7 1st active ingredient	
drug7 strength 1st active ingredient	
drug7 unit 1st active ingredient	
drug7 2nd active ingredient	
drug7 strength 2nd active ingredient	
drug7 unit 2nd active ingredient	
drug7 3rd active ingredient	
drug7 strength 3rd active ingredient	
drug7 unit 3rd active ingredient	
drug7 4th active ingredient	
drug7 strength 4th active ingredient	
drug7 unit 4th active ingredient	
drug7 5th active ingredient	
drug7 strength 5th active ingredient	
drug7 unit 5th active ingredient	
drug8 script	◯ Dispensed ◯ Prescribed
drug8 name	

drug8 nappi	
drug8 format	
drug8 form	
drug8 pack	
drug8 schedule	
drug8 quantity	
drug8 atc	
drug8 1st active ingredient	
drug8 strength 1st active ingredient	
drug8 unit 1st active ingredient	
drug8 2nd active ingredient	
drug8 strength 2nd active ingredient	
drug8 unit 2nd active ingredient	
drug8 3rd active ingredient	
drug8 strength 3rd active ingredient	
drug8 unit 3rd active ingredient	
drug8 4th active ingredient	
drug8 strength 4th active ingredient	

drug8 unit 4th active ingredient	
drug8 5th active ingredient	
drug8 strength 5th active ingredient	
drug8 unit 5th active ingredient	

APPENDIX M: Validation Tool

Validation Instrument

vid	_____
number of drugs	_____
Drug 1: [dname1] [strength1] [unit1] [form1] Nappi: [nappi1]Quantity: [quantity1] [script1]	
Drug 1: [dname1] [form1] Nappi: [nappi1]Quantity: [quantity1] [script1]	
Drug 1 checked	☐ Checked
Corrections:	
drug1 name	_____
drug1 nappi	_____
drug1 strength	_____
drug1 unit	_____
drug1 form	_____
drug1 quantity	_____
drug1 dispensed/prescribed?	◯ Dispensed ◯ Prescribed
CHECK YOUR CORRECTIONS. At least one of your corrected fields is the same as the original data	
Drug 2: [dname2] [strength2] [unit2] [form2] Nappi: [nappi2]Quantity: [quantity2] [script2]	
Drug 2: [dname2] [form2] Nappi: [nappi2]Quantity: [quantity2] [script2]	
Drug 2 checked	☐ Checked
Corrections:	
drug2 name	_____

drug2 nappi	
drug2 strength	
drug2 unit	
drug2 form	
drug2 quantity	
drug2 dispensed/prescribed?	◯ Dispensed ◯ Prescribed

CHECK YOUR CORRECTIONS.
At least one of your corrected fields is the same as the original data

Drug 3:
[dname3] [strength3] [unit3] [form3] Nappi: [nappi3]Quantity: [quantity3] [script3]

Drug 3:
[dname3] [form3] Nappi: [nappi3]Quantity: [quantity3] [script3]

Drug 3 checked	☐ Checked
Corrections:	
drug3 name	
drug3 nappi	
drug3 strength	
drug3 unit	
drug3 form	
drug3 quantity	
drug3 dispensed/prescribed?	◯ Dispensed ◯ Prescribed

CHECK YOUR CORRECTIONS.
At least one of your corrected fields is the same as the original data

Drug 4:
[dname4] [strength4] [unit4] [form4] Nappi: [nappi4]Quantity: [quantity4] [script4]

Drug 4:
[dname4] [form4] Nappi: [nappi4]Quantity: [quantity4] [script4]

Drug 4 checked ☐ Checked

Corrections:

drug4 name

drug4 nappi

drug4 strength

drug4 unit

drug4 form

drug4 quantity

drug4 dispensed/prescribed? ◯ Dispensed ◯ Prescribed

CHECK YOUR CORRECTIONS.
At least one of your corrected fields is the same as the original data

Drug 5:
[dname5] [strength5] [unit5] [form5] Nappi: [nappi5]Quantity: [quantity5] [script5]

Drug 5:
[dname5] [form5] Nappi: [nappi5]Quantity: [quantity5] [script5]

Drug 5 checked ☐ Checked

Corrections:

drug5 name

drug5 nappi

drug5 strength

drug5 unit

drug5 form	_____
drug5 quantity	_____
drug5 dispensed/prescribed?	◯ Dispensed ◯ Prescribed
CHECK YOUR CORRECTIONS. At least one of your corrected fields is the same as the original data	
Drug 6: [dname6] [strength6] [unit6] [form6] Nappi: [nappi6]Quantity: [quantity6] [script6]	
Drug 6: [dname6] [form6] Nappi: [nappi6]Quantity: [quantity6] [script6]	
Drug 6 checked	☐ Checked
Corrections:	
drug6 name	_____
drug6 nappi	_____
drug6 strength	_____
drug6 unit	_____
drug6 form	_____
drug6 quantity	_____
drug6 dispensed/prescribed?	◯ Dispensed ◯ Prescribed
CHECK YOUR CORRECTIONS. At least one of your corrected fields is the same as the original data	
Drug 7: [dname7] [strength7] [unit7] [form7] Nappi: [nappi7]Quantity: [quantity7] [script7]	
Drug 7: [dname7] [form7] Nappi: [nappi7]Quantity: [quantity7] [script7]	
Drug 7 checked	☐ Checked
Corrections:	

drug7 name	_____
drug7 nappi	_____
drug7 strength	_____
drug7 unit	_____
drug7 form	_____
drug7 quantity	_____
drug7 dispensed/prescribed?	◯ Dispensed ◯ Prescribed

CHECK YOUR CORRECTIONS.
At least one of your corrected fields is the same as the original data

APPENDIX N: Data Entry Tool

Data Entry

vid _____

Date of data collection _____ (DD-MM-YYYY)

Script Details

Script Identity
- ◯ Dispensed
- ◯ Prescribed

Legal requirements for a label on the original container from the manufacturer

Was the date of dispensing present ?	◯ Yes ◯ No
Was the approved name of the medicine present on the label?	◯ Yes ◯ No
Was the name of the person for whose treatment such medicine is sold present on the label?	◯ Yes ◯ No
Were the directions in regard to the manner in which such medicine should be used present?	◯ Yes ◯ No
Was the name of the person authorized to sell such a medicine present?	◯ Yes ◯ No
Was the business address of the person authorized to sell such a medicine present?	◯ Yes ◯ No
Was the reference number present on the label?	◯ Yes ◯ No

Label for a dispensed medicine which has undergone pre-packing

Was the packaging date present ?	◯ Yes ◯ No
Was the name of the patient present on the label?	◯ Yes ◯ No
Was the approved name of the medicine provided on the label?	◯ Yes ◯ No
Was the batch number provided on the label?	◯ Yes ◯ No
Was the strength provided on the label?	◯ Yes ◯ No

Was the quantity provided on the label?	◯ Yes ◯ No
Was the expiry date of the medicine provided on the label?	◯ Yes ◯ No
Was the name of the institution responsible for pre-packing present on the label?	◯ Yes ◯ No
Was the address of the institution responsible for pre-packing present on the label?	◯ Yes ◯ No
Were the directions of use for the medicine present on the label?	◯ Yes ◯ No
Were the storage conditions and/or warnings provided on the label?	◯ Yes ◯ No
Was the reference number present on the label?	◯ Yes ◯ No

Legal requirements for a prescription	
Was the Identification (ID) number of the patient present?	◯ Yes ◯ No
Was the date present on the prescription?	◯ Yes ◯ No
Was the prescriber's name present?	◯ Yes ◯ No
Was the prescriber's address present?	◯ Yes ◯ No
Was the prescriber's signature present?	◯ Yes ◯ No
Were the prescriber's qualifications present?	◯ Yes ◯ No
Was the prescriber's MP number present?	◯ Yes ◯ No
Were the prescriber's contact details present?	◯ Yes ◯ No
Was the patient's name present?	◯ Yes ◯ No
Was the patient's address present?	◯ Yes ◯ No
Was the patient's age present?	◯ Yes ◯ No

Was the patient's body weight present?	◯ Yes ◯ No
Was the patient's gender present?	◯ Yes ◯ No
Was the approved name of the medicine present?	◯ Yes ◯ No
Was the dosage form/s present?	◯ Yes ◯ No
Was the strength/s of the medicine/s present?	◯ Yes ◯ No
Was the quantity of the medicine/s present?	◯ Yes ◯ No
Were the instructions of taking the medicine/s present?	◯ Yes ◯ No

Defined Daily Dose (DDD) requirements

Was the dose provided in alignment with the Defined Daily Dose (DDD)?	◯ Yes ◯ No

Dosage Intervals

Were the dosage intervals provided for the drug/s on this script such as: D, BD, TDS and QID?	◯ Yes ◯ No

Duration of Therapy

Was the duration of therapy provided for the medicine/s on this script such as: 5/7, 2/52 and 1/12 ?	◯ Yes ◯ No

Quantity

Was the quantity of the medicine/s present?	◯ Yes ◯ No

Antibiotics

Were there any antibiotics given for this script?	◯ Yes ◯ No
If yes, how many antibiotics were given on this script?	_____

Drug to Drug Interactions

Were there any drug to drug interactions on this script?	◯ Yes ◯ No
If yes, how many drug to drug interactions were present for this script?	_____

Interaction 1

Interaction 1: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 1: Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 1: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious
Interaction 1 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

Interaction 2

Interaction 2: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 2: Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 2: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious

Interaction 2 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

Interaction 3

Interaction 3: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 3: Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 3: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious

Interaction 3 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

Interaction 4

Interaction 4: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 4: Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 4: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious

Interaction 4 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

Interaction 5	
Interaction 5: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 5: Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 5: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious

Interaction 5 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

Interaction 6

Interaction 6: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 6; Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 6: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious

Interaction 6 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

Interaction 7

Interaction 7: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 7: Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 7: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious

Interaction 7 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

Interaction 8

Interaction 8: Name of drug1 or Active Pharmaceutical Ingredient 1	_____
Interaction 8: Name of drug2 or Active Pharmaceutical Ingredient 2	_____
Interaction 8: What was the type of interaction?	◯ Minor ◯ Moderate/Monitor Closely ◯ Serious

Interaction 8 Explanation	◯ Increased sedation ◯ Antagonistic action ◯ Levels of one drug increased due to metabolic enzymes ◯ Levels of one drug decreased due to metabolic enzymes ◯ Levels of one drug increased due to metabolic enzymes with increased effects of the drug ◯ Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug ◯ Levels of one drug increased with increased risk of toxicity ◯ Levels of one drug increased by the other drug directly ◯ Levels of one drug decreased by the other drug directly ◯ Increased risk of toxicity ◯ Levels of one drug increased due to absorption interactions ◯ Levels of one drug decreased due to absorption interactions ◯ Levels of one drug decreased due to protein binding ◯ Levels of one drug increased due to renal excretion interactions ◯ Levels of one drug decreased due to renal excretion interactions

APPENDIX O: List of all medicines in this study

Table O1: Prescribing patterns of medicines in the private sector

Drug name (Trade name/s in brackets + strength + dosage form)	Frequency	Defined Daily Dose (DDD) in mg	Route of drug admin-istration	Dispen ser	ATC code	Sector
PENICILLINS						
1.Amoxicillin (Allmox 250mg capsules, Allmox 500mg capsules, Amoxicap 250mg capsules, Amoxil 250mg capsules, Amoxil 500mg capsules, Adco-Amoxycillin 500mg capsules, Austell-Amoxicillin 250mg capsules, Austell-Amoxicillin 500mg capsules, Betamox 250mg capsules, Betamox 500mg capsules)	**21**	**1500**	**Oral**	**Non-disp-ensing doct-or (NDD)**	**J01CA04**	**Private**
2.Amoxicillin and Flucloxacillin combination (Macropen 500mg capsules)	**1**	**1500**	**Oral**	**NDD**	**J01CA**	**Private**
PENICILLIN/BETA LACTAMASE INHIBITOR COMBINATION						
1.Amoxicillin + Clavulanic acid (Adco-Amoclav 625mg tablets, Adco Amoxyclav 1000mg tablets, Amoclan 1000mg tablets, Augmaxcil 375mg tablets, Augmaxcil 625mg tablets, Augmentin 375mg tablets, Augmentin 1000mg tablets, Auro amoxiclav 375mg tablets, Auro amoxiclav 1000mg tablets, Austell Co-amoxiclav 375mg suspension, Austell Co-amoxiclav 1000mg suspension,	**49**	**1500**	**Oral**	**NDD**	**J01CR02**	**Private**

Clamentin 375mg tablets, Clamentin 1000mg tablets, Forcid solutab 875/125 tablets, Ranclav 625mg tablets, Sandoz Co-amoxyclav 375mg tablets, Sandoz Co-amoxyclav 1000mg tablets)						
MACROLIDES						
1.Azithromycin (Aspen azithromycin 500mg tablets, Azithromycin 500mg Zydus tablets, Zithrogen 500mg tablets, Zithromax 500mg tablets)	**12**	**300**	**Oral**	**NDD**	**J01FA10**	**Private**
2.Clarithromycin (Clacee 500mg tablets, Klacid XL 10 500mg tablets, Klarithran 500mg tablets)	**18**	**500**	**Oral**	**NDD**	**J01FA09**	**Private**
3.Erythromycin (Purmycin 250mg suspension)	**1**	**1000**	**Oral**	**NDD**	**J01FA01**	**Private**
FLUOROQUINOLONES						
1.Ofloxacin (Exocin 3mg/ml eye drops)	**1**	**400**	**Oral**	**NDD**	**J01MA01**	**Private**
2.Moxifloxacin (Avelon tabs 400mg tablets, Moxibay tablets 400mg)	**2**	**400**	**Oral**	**NDD**	**J01MA14**	**Private**
CEPHALOSPORINS						
1.Cefuroxime (Zinnat tablets 500mg)	**1**	**500**	**Oral**	**NDD**	**J01DC02**	**Private**
2.Cefpodoxime (Orelox 200mg tablets)	**2**	**400**	**Oral**	**NDD**	**J01DD13**	**Private**
KETOLIDES						
1.Telithromycin (Ketek 400mg tablets)	**1**	**800**	**Oral**	**NDD**	**J01FA15**	**Private**
CORTICOSTEROIDS						
1.Prednisone (Meticorten 5mg tablets, Be-Tabs prednisone 5mg tablets, Panafcort 5mg tablets, Prednisone 5mg	**44**	**10**	**Oral**	**NDD**	**H02AB07**	**Private**

tablets, Pulmison 20mg tablets, Trolic 5mg tablets)						
2.Betamethasone (Betanoid 0.5mg tablets, Celestamine 0.25mg tablets)	**30**	**1.5**	**Oral**	**NDD**	**H02AB01**	**Private**
3.Fluticasone (Avamys 27.5 mcg nasal spray, Flixonase 50 mcg Aqueous nasal spray, Flomist 50 mcg nasal spray, Foxair Accuhaler 50/250 mcg)	**21**	**0.2**	**Nasal**	**NDD**	**R01AD08**	**Private**
4.Mometasone (Nasonex 50mcg Aqueous nasal spray, Nexomist 50µg nasal spray, Rinelon 50mcg Aqueous nasal spray)	**9**	**0.2**	**Nasal**	**NDD**	**R01AD09**	**Private**
5.Beclometasone (Beclate aquanase 50mcg nasal spray)	**2**	**0.4**	**Nasal**	**NDD**	**R01AD01**	**Private**
6.Ciclesonide (Omnair 50µg nasal spray)	**4**	**0.2**	**Nasal**	**NDD**	**R01AD13**	**Private**
7.Methylpredni-solone (Medrol 4mg tablets)	**2**	**7.5**	**Oral**	**NDD**	**H02AB04**	**Private**
ANTIHISTAMINES						
1.Chlorpheni-ramine (Allergex 4mg tablets, Rhineton 4mg tablets)	**14**	**12**	**Oral**	**NDD**	**R06AB02**	**Private**
2.Cetirizine (Allecet 10mg tablets, Allermine 10mg tablets, Austell-Cetirizine 10mg tablets, Sandoz-Cetirizine 10mg tablets, Sensahist 10mg tablets, Texa-allergy tablets 10mg, Trantrin tablets 10mg, Zetop 10mg tablets)	**9**	**10**	**Oral**	**NDD**	**R06AE07**	**Private**
3.Loratadine (Allergex non drowsy 10mg tablets, Apex-loratadine	**7**	**10**	**Oral**	**NDD**	**R06AX13**	**Private**

10mg tablets, AP loratadine 10mg tablets, Laura 10mg tablets)						
4.Desloratadine (Dazit 5mg tablets, Deselex 5mg tablets, Desotab 5mg tablets)	**8**	**5**	**Oral**	**NDD**	**R06AX27**	**Private**
5.Levocetirizine (Allerway 5mg tablets, Xyzal 5mg tablets)	**11**	**5**	**Oral**	**NDD**	**R06AE09**	**Private**
6.Promethazine (Phernegan 10mg tablets, Phensedyl cough linctus 3.6mg/5ml)	**4**	**25**	**Oral**	**NDD**	**R06AD02**	**Private**
7.Rupatadine (Rupanase 10mg tablets)	**1**	**10**	**Oral**	**NDD**	**R06AX28**	**Private**
ANILINE ANALGESICS						
1.Paracetamol (Parapane 500mg tablets)	**1**	**3000**	**Oral**	**NDD**	**N02BE01**	**Private**
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)						
1.Diclofenac (Diclofenac 25mg Biotech tablets, Diclofenac Sodium 50mg tablets)	**5**	**100**	**Oral**	**NDD**	**M01AB05**	**Private**
2.Flurbiprofen (Strepsils Intensive 8.75mg lozenges)	**2**	**200**	**Oral**	**NDD**	**M01AE09**	**Private**
NASAL DECONGESTANTS						
1. Oxymetazoline (Iliadin nose drops 0.5mg/ml, Nazene Z Nasal Spray 0.5mg/ml)	**7**	**0.4**	**Nasal**	**NDD**	**R01AA05**	**Private**
2.Phenylephrine (Adco-naphensyl nose drops 100mg/10ml)	**1**	**4**	**Nasal**	**NDD**	**R01AA04**	**Private**
3.Xylometazoline (Otrivin adult nasal spray 1mg/ml)	**1**	**0.8**	**Nasal**	**NDD**	**R01AA07**	**Private**
4.Pseudo-ephedrine (Sudafed sinus 60mg tablets)	**1**	**240**	**Oral**	**NDD**	**R01BA02**	**Private**
MUCOLYTICS						
1.Acetylcysteine (ACC 200 effervescent tablets, AMUCO 200mg effervescent tablets)	**10**	**1600**	**Oral**	**NDD**	**R05CB01**	**Private**

2.Carbocisteine (Betaphlem syrup 250mg/5ml, Flemgo 250mg/5ml syrup, Mucospect 250mg/5ml syrup)	**3**	**1500**	**Oral**	**NDD**	**R05CB03**	**Private**
LEUKOTRIENE RECEPTOR ANTAGONISTS						
1.Montelukast (Lumont 10mg tablets, MONTE-AIR 10mg tablets, SINTAIR 10mg tablets, Topraz 10mg tablets)	**10**	**10**	**Oral**	**NDD**	**R03DC03**	**Private**
SHORT-ACTING BETA AGONISTS						
1.Salbutamol tablets (Venteze 4mg tablets)	**1**	**12**	**Oral**	**NDD**	**R03CC02**	**Private**
2.Inhaled Salbutamol (Asthavent 100mcg inhaler)	**1**	**0.8**	**Inhalation**	**NDD**	**R03AC02**	**Private**
NEURAMINIDASE INHIBITORS						
1. Oseltamivir (Tamiflu 30mg tablets)	**1**	**150**	**Oral**	**NDD**	**J05AH02**	**Private**
COMPLEMENTARY MEDICINES						
1.A Vogel Sore Throat Spray 30ml (863.3mg of Echinacea purpurea herb, 45.5mg of Echinacea purpurea root, 430mg of Sage leaves, Sorbitol 407mg, Ethanol 370mg, Soy lecithin 20mg and Sucrose laurate 5mg)	**2**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**
2. Echinaforce® drops 100ml (Echinacea purpurea herb 95% and Echinacea purpurea root 5%)	**1**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**
3.Karvol® Decongestant Inhalation 10 capsules (Combination of oils)	**2**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**
4.Prospan cough syrup 100ml (0.7 g of dried Ivy leaf extract, 0.134 g of	**14**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**

potassium sorbate and other ingredients)						
5.Sinupret forte 20 capsules (Gentian root, elder flowers, and other ingredients)	**3**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**
PROBIOTICS						
1.Inteflora 250 capsules (*Saccharomyces Boulardii and other ingredients)*	**11**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**
2.ProbiFlora Adult 4 Strain 30 VegeCaps (*Lactobacillus acidophilus* and other ingredients)	**7**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**
3.Reuterina acute tablets (*Lactobacillus reuteri and other ingredients)*	**3**	**N/A**	**Oral**	**NDD**	**N/A**	**Private**
VITAMINS						
1.Vitamin C (Clicks Vitamin C 500 mg tablets)	**2**	**200**	**Oral**	**NDD**	**A11GA01**	**Private**
MULTIVITAMINS WITH MINERALS						
1.Bonvit Soft Gel capsules (Vitamins and minerals)	**2**	**Fixed dose**	**Oral**	**NDD**	**A11AA03**	**Private**
MULTIVITAMINS						
1.Vital Multivitamin capsules (Multivitamin solution)	**1**	**Fixed dose**	**Oral**	**NDD**	**R05X**	**Private**
ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIS)						
1.Lisinopril (Sinopren 20 tabs 20mg tablets)	**1**	**10**	**Oral**	**NDD**	**C09AA03**	**Private**
COMBINED ORAL CONTRACEPTIVES (COCS)						
1.Famynor tablets (Norgestrel 0.5mg/ Ethinyl Estradiol 0.05mg)	**1**	**N/A**	**Oral**	**NDD**	**G03AA06**	**Private**
IMIDAZOLE ANTIFUNGALS						
1.Fluconazole (Fluzol 200mg capsules)	**3**	**200**	**Oral**	**NDD**	**J02AC01**	**Private**
2.Miconazole (Daktarin oral gel 20mg/g)	**1**	**200**	**Oral**	**NDD**	**A01AB09**	**Private**

PROTON PUMP INHIBITORS (PPIS)						
1.Omeprazole (Omez 20mg capsules)	**2**	**20**	**Oral**	**NDD**	**A02BC01**	**Private**
2.Pantoprazole (Prazoloc 40mg tablets)	**2**	**40**	**Oral**	**NDD**	**A02BC02**	**Private**
OTHER COLD PREPARATIONS						
1.Glyco Thymol Co Mouthwash 100ml (Contains Glyco-thymoline and other ingredients)	**1**	**Fixed dose**	**Oral**	**NDD**	**R05X**	**Private**
2.Betadine Mouthwash and gargle 125ml (1% Povidone-iodine)	**1**	**Fixed dose**	**Oral**	**NDD**	**R05X**	**Private**
3.Antibiotic/Organo chlorine compound (Chloramex Opthalmic Ointment 3.5 G - Chloramphenicol 10mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**D06AX**	**Private**
4.Ammonium chloride/Expectorant (Expigen 200ml cough syrup - Sorbimacrogol laurate 300 36.33 mg/Ammonium chloride - 34.00 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**R05X**	**Private**
5.Aniline analgesic/ NSAID (Ibupain capsules – Ibuprofen 200 mg/Paracetamol 250 mg; Mypaid capsules -Ibuprofen 200 mg/Paracetamol 250 mg)	**3**	**Fixed dose**	**Oral**	**NDD**	**M01AE**	**Private**
6.Antihistamine /Nasal decong-estant (Actifed cold tablets – Pseudoephedrine 30 mg/5ml / Tripolidine 1.25 mg; Decofed tablets - Pseudoephedrine 30 mg/5ml / Tripolidine 1.25 mg; Demazin NS Repetabs – Pseudoephedrine 120 mg/Loratadine 5 mg)	**3**	**Fixed dose**	**Oral**	**NDD**	**R06AX**	**Private**
7.Antihistamine	**15**	**Fixed**	**Oral**	**NDD**	**R03DA**	**Private**

/Xanthine (Alcophyllex syrup 100ml/200ml - Theophylline 16.667 mg/5ml / Diphenhydramine HCl 6.666 mg/5ml)		**dose**				
8.Antiseptic/Local anaesthetic (Cepacol Plus Original Lozenges - Cetylpyridinium chloride 1.399 mg/ Benzocaine 10 mg; Cepacol Plus Blackcurrant Lozenges - Cetylpyridinium chloride 1.399 mg/ Benzocaine 10 mg; Medi-Keel A Honey and Lemon Throat Lozenges - Cetylpyridinium chloride 1.5 mg/ Benzocaine 12 mg; Orochlor 100ml – Benzocaine 267 mg/100ml / Chlorhexidine 1mg/100ml)	**4**	**Fixed dose**	**Oral**	**NDD**	**R02AD**	**Private**
9.Bronchodilator /Mucolytic (Flemeze Bronchodilatory syrup 100ml - Bromhexine Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml; Bisolvon Linctus DA 100ml -Bromhexine Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml; Bronkese Compound Linctus 100ml - Bromhexine Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml; Adco-linctopent syrup 100ml/200ml - Bromhexine	**12**	**Fixed dose**	**Oral**	**NDD**	**R05CB**	**Private**

Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml)						
10.Cortico-steroid/Long -acting beta agonist (Symbicord turbuhaler 160:45µg/ dose - Formoterol Fumarate Dihyrate 4.5 mcg/ Budesonide 160 mcg)	**2**	**Fixed dose**	**Inhalation**	**NDD**	**R03BA**	**Private**
11.NSAID/Nasal decongestant (Advil cold & sinus tablets – Ibuprofen 200 mg/Pseudoephedrine 30 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**
12.Opioid/Nasal Decongestant (Pholtex plus 100ml/200ml - Pholcodine 5 mg/5ml / Phenylephrine Hydrochloride 3.3 mg/5ml)	**14**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**
13.Aniline analgesic/ Antihistamine/ Nasal decongestant (Famucaps – Paracetamol 300 mg/ Chlorpheniramine maleate 2 mg/ Phenylephrine HCL 5 mg)	**4**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**
14.Aniline analgesic/ Antihistamine/ Vitamin (Efferflu C Cold & Flu - Vitamin C 250 mg/ Chlorphenamine Maleate 2 mg/ Paracetamol 500 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**R06AB**	**Private**
15. Antihistamine /Aminoglycoside /Nasal Decongestant (Vibrocil nasal gel – Dimetindene 25 mg, Phenylephrine 250 mg, Neomycin 350 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**R01AX**	**Private**

16.Antiseptic/ NSAID (Andolex-C Raspberry Sore Throat lozenges- Benzydamine hydrochloride 3 mg/Cetylpyridinium CL 1.33 mg)	**4**	**Fixed dose**	**Oral**	**NDD**	**R02AD**	**Private**
17. Antihistamine /Expectorant /Nasal Decongestant (Sinuclear cough syrup 100ml - Pseudoephedrine HCI 30 mg/5ml / Triprolidine HCI 1.25 mg/5ml / Dextromethorphan Hydrobromide 10 mg/5ml)	**3**	**Fixed dose**	**Oral**	**NDD**	**R06AX**	**Private**
18.Expectorant/ Vitamin derivative /Ammonium Chloride (Broncol cough linctus 100ml/200ml - Ammonium Chloride 180 mg/10ml / Dexpanthenol 100 mg/10ml / Dextromethorphan HBr 30 mg/10ml)	**2**	**Fixed dose**	**Oral**	**NDD**	**R05FA**	**Private**
19.Opioid/Aniline analgesic/ Carbamate (Synaleve capsules - Codeine Phosphate 8 mg/ Meprobamate 200 mg/ Paracetamol 400 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**N02BE**	**Private**
20. Opioid/Aniline analgesic/ NSAID (Ibupain forte capsules – Paracetamol 250 mg/Codeine 10 mg/Ibuprofen 200 mg; Mybucod tablets - Paracetamol 350 mg/Codeine 10 mg/Ibuprofen 200 mg; Mybulen capsules - Paracetamol 250	**9**	**Fixed dose**	**Oral**	**NDD**	**M01AE N02BE**	**Private**

mg/Codeine 10 mg/Ibuprofen 200 mg; Myprodol tablets - Paracetamol 250 mg/Codeine 10 mg/Ibuprofen 200 mg; Genpayne capsules - Paracetamol 250 mg/ Codeine 10 mg/Ibuprofen 200 mg)						
21.Opioid/Aniline analgesic/ Antihistamine (Doxy Co tablets - Paracetamol 450 mg/ Codeine 10 mg/Doxylamine 5 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**N02BE**	**Private**
22.Organic Polymer/Vitamin/Mineral (Biobalance Immunova – Carbohydrate Derived Fulvic acid 300 mg/Vitamin C 250 mg/Zinc 5 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**R05X**	**Private**
23.Antihistamine/ Ammonium chloride/ Xanthine (Dilinct syrup 100ml/200ml - Etofylline nicotinate 105.5 mg/ Ammonium Chloride 410.5 mg/ Diphenhydramine 42.2 mg)	**10**	**Fixed dose**	**Oral**	**NDD**	**R06AA**	**Private**
24.Antihistamine/ Ammonium Chloride/ Sodium citrate (Bencough expectorant syrup 100ml - Ammonium chloride 136 mg/ Sodium citrate 65 mg/ Diphenhydramine 14 mg; Phenorant syrup 100ml/200ml - Ammonium chloride 130 mg/5 ml / Sodium citrate 54.165mg/5ml /	**13**	**Fixed dose**	**Oral**	**NDD**	**R06AA**	**Private**

Diphenhydramine 13.33 mg/5ml; Relief-Coff EXP 100ml/200ml - Ammonium chloride 136 mg/5 ml / Sodium citrate 56 mg/5ml / Diphenhydramine 14 mg/5ml; Clear cough 100ml - Ammonium chloride 135 mg/5 ml / Sodium citrate 55 mg/5ml / Diphenhydramine 14.1 mg/5ml)						
25.Vitamin/Nasal Decongestant/ Aniline Analgesic (Corenza Para-C Effervescent - Phenylephrine Hydrochloride 10 mg/ Paracetamol 650 mg/ Vitamin C 250 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**
26.Xanthine/ Aniline Analgesic/ Nasal Decongestant (Sinuend tablets – Caffeine 20 mg/ Paracetamol 200 mg/ Ephedrine 6 mg)	**4**	**Fixed dose**	**Oral**	**NDD**	**R06AA**	**Private**
27. Xanthine/ Aniline Analgesic/ Nasal Decongestant/ Antihistamine (Flusin tablets - Caffeine 20 mg/ Paracetamol 200 mg/Pseudoephedrine 6 mg Chlorpheniramine 2 mg; Sinucon tablets - Caffeine 20 mg/ Paracetamol 200 mg/Pseudoephedrine 6 mg Chlorpheniramine 2 mg; Histacon capsules - Caffeine 30 mg/Paracetamol	**14**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**

200 mg/Phenylephrine 5 mg Chlorpheniramine 2 mg)						
28. Expectorant/Ammonium Chloride (Benylin Original 100ml/200ml - Ammonium Chloride 125 mg/5ml / Dextromethorphan 12.5 mg/5ml)	**9**	**Fixed dose**	**Oral**	**NDD**	**R05CA**	**Private**
29. Vitamin/ Aniline Analgesic/ Nasal Decongestant/ Antihistamine (Degoran C capsules - Caffeine 30 mg/Paracetamol 300 mg/Phenylephrine 5 mg Chlorpheniramine 2 mg/ Ascorbic acid 75 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**
30. Xanthine/ Aniline Analgesic/ Opioid/ Carbamate (Adco-Salterpyn tablets - Caffeine Anhydrous 32 mg/ Meprobamate 150 mg/ Codeine phosphate 8 mg/ Paracetamol 320 mg; Stilpane tablets – Caffeine 32 mg/ Meprobamate 150 mg/ Codeine phosphate 8 mg/ Paracetamol 320 mg)	**7**	**Fixed dose**	**Oral**	**NDD**	**N02BE**	**Private**
31. Ammonium chloride/ Sodium citrate/Opioid/ Nasal decongestant/ Antihistamine (Coughcod Senior 200ml syrup – Mepyramine 6.25 mg/5ml / Ammonium Chloride 62.5	**1**	**Fixed dose**	**Oral**	**NDD**	**R05DA**	**Private**

mg/5ml / Codeine 5 mg/5ml / Ephedrine 5 mg/5ml / Sodium citrate 25 mg/5ml)						
32.Vitamin/ NSAID/ Opioid/ Antihistamine (Coryx effervescent tablets - Chlorpheniramine Maleate 4 mg/ Pseudoephedrine HCl 50 mg/ Ascorbic acid 330 mg/Aspirin 600 mg)	**6**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**
33.Vitamin/ Xanthine/ Aniline analgesic/Antihistamine/ Nasal decongestant (Flustat capsules - Ascorbic Acid 75 mg/Paracetamol 300 mg/Caffeine 30 mg/Chlorpheniramine maleate 2 mg/Phenylephrine HCL 5 mg)	**6**	**Fixed dose**	**Oral**	**NDD**	**R01BA**	**Private**
34.Antihistamine/ Xanthine/ Aniline analgesic/ Opioid (Tensopyn tablets - Doxylamine Succinate 5 mg/ Paracetamol 450 mg/ Caffeine 30 mg/ Codeine Phosphate 10 mg)	**1**	**Fixed dose**	**Oral**	**NDD**	**N02BE**	**Private**
35.Opioid/ Expectorant/ Ammonium Chloride (Benylin with codeine 100ml/200ml - Ammonium Chloride 125 mg/5ml / Codeine 10 mg/5ml / Diphenhydramine 12.5 mg/5ml)	**2**	**Fixed dose**	**Oral**	**NDD**	**R05FA**	**Private**

Table O2: Dispensing patterns of medicines in the private sector

Drug name	Frequency	Defined	Route of	Dispen	ATC code	Sector

		Daily Dose (DDD) in mg	**drug admin-istration**	**ser**		
PENICILLINS						
1.Amoxicillin (Allmox 500mg capsules, Amoxil 250mg capsules, Amoxil 500mg capsules, Adco-amoxycillin 500mg capsules, Austell-amoxicillin 250mg capsules, Austell-amoxicillin 500mg capsules, Betamox 250mg capsules, Betamox 500mg capsules, Moxan 250mg capsules, Moxymax 250mg capsules, Moxymax 500mg capsules, Moxypen 250mg capsules, Moxypen 500mg capsules, Mymox 500mg capsules, Zoxil 500mg capsules)	**95**	**1500**	**Oral**	**Disp-ensing doct-or (DD)**	**J01CA04**	**Private**
PENICILLIN/BETA LACTAMASE INHIBITOR COMBINATION						
1.Amoxicillin + Clavulanic acid (Adco Amoclav 625mg tablets, Adco Amoxyclav 1000mg tablets, Augmaxcil 375mg tablets, Augmaxcil 625mg tablets, Auro amoxiclav 375mg tablets, Auro amoxiclav 1000mg tablets, Austell-Co-amoxiclav 375mg suspension, Austell-Co-amoxiclav 1000mg suspension, Clamentin 375mg tablets, Clamentin 1000mg tablets, Ranclav 625mg tablets, Ranclav 1g tablets, Sandoz coamoxyclav 375mg tablets, Sandoz	**22**	**1500**	**Oral**	**DD**	**J01CR02**	**Private**

coamoxyclav 1000mg tablets)						
MACROLIDES						
1.Erythromycin (Adco Erythromycin 250mg capsules, Eryko-250 tablets, Purmycin 250mg capsules)	**11**	**1000**	**Oral**	**DD**	**J01FA01**	**Private**
FLUOROQUINOLONES						
1.Ciprofloxacin (Austell-Ciprofloxacin 500mg tablets, Cifran 500mg tablets)	**5**	**1000**	**Oral**	**DD**	**J01MA02**	**Private**
2.Ofloxacin (Apex-Ofloxacin 400mg tablets)	**1**	**400**	**Oral**	**DD**	**J01MA01**	**Private**
SULPHONAMIDE/FOLIC ACID INHIBITOR COMBINATIONS						
1.Sulfame-thoxazole/Tri-Methoprim (Purbac adult 400/80mg tablets, Bactrim adult 400/80mg tablets, Lagatrim 400/80mg tablets)	**10**	**N/A**	**Oral**	**DD**	**J01EE01**	**Private**
CEPHALOSPORINS						
1.Cefalexin (Ranceph 500mg capsules)	**2**	**2000**	**Oral**	**DD**	**J01DB01**	**Private**
NITROIMIDAZOLES						
1.Metronidazole (Anaerobyl 400mg tablets, Flagyl 400mg tablets, Metazol 200mg tablets)	**3**	**2000**	**Oral**	**DD**	**P01AB01**	**Private**
TETRACYCLINES						
1.Doxycycline (Cyclidox 100mg capsules, Doxycyl 100mg capsules, Doxytet 100mg capsules)	**3**	**100**	**Oral**	**DD**	**J01AA02**	**Private**
CORTICOSTEROIDS						
1.Prednisone (Meticorten 5mg tablets, Be-Tabs prednisone 5mg tablets, Panafcort 5mg tablets, Prednisone 5mg tablets, Pulmison 20mg tablets, Trolic 5mg tablets)	**98**	**10**	**Oral**	**DD**	**H02AB07**	**Private**

2.Betamethasone (Betanoid 0.5 mg tablets, Celestamine 0.25 mg tablets)	**4**	**1.5**	**Oral**	**DD**	**H02AB01**	**Private**
3.Fluticasone (Avamys 27.5 mcg nasal spray, Flonase 50 mcg Aqueous nasal spray)	**2**	**0.2**	**Nasal**	**DD**	**R01AD08**	**Private**
4.Mometasone (Kleernaze Nasal spray 30ml)	**1**	**0.2**	**Nasal**	**DD**	**R01AD09**	**Private**
5.Beclometasone (Beclate aquanase 50mcg nasal spray)	**3**	**0.4**	**Nasal**	**DD**	**R01AD01**	**Private**
ANTIHISTAMINES						
1.Chlorpheni-ramine (Allergex 4mg tablets, Rhineton 4mg tablets)	**12**	**12**	**Oral**	**DD**	**R06AB02**	**Private**
2.Cetirizine (Allecet 10mg tablets, Allermine 10mg tablets, Austell-cetirizine 10mg tablets, Sandoz-cetirizine 10mg tablets, Sensahist 10mg tablets, Texa-allergy 10mg tablets, Trantrin 10mg tablets, Zetop 10mg tablets)	**17**	**10**	**Oral**	**DD**	**R06AE07**	**Private**
3.Loratadine (Allergex non drowsy 10mg tablets, Apex-loratadine 10mg tablets, AP loratadine 10mg tablets, Laura 10mg tablets, Lorano 10mg tablets, Lorhay 10mg tablets, Rhinigine 10mg tablets)	**12**	**10**	**Oral**	**DD**	**R06AX13**	**Private**
4.Desloratadine (Dazit 5mg tablets, Deselex 5mg tablets, Desotab 5mg tablets)	**4**	**5**	**Oral**	**DD**	**R06AX27**	**Private**
ANILINE ANALGESICS						
1.Paracetamol (Paracet 500mg tablets, Paracetamol 500mg tablets, Parapane 500mg	**41**	**3000**	**Oral**	**DD**	**N02BE01**	**Private**

tablets, Adco Prolief 500mg tablets, Adco-napamol 500mg tablets, Austell-paracetamol 500mg tablets, Painamol 500mg tablets, Panado 500mg tablets, Pacimol 500mg tablets)						
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)						
1.Ibuprofen (Ibucine 200mg tablets, Brufen 200mg tablets, Ibunate 200mg tablets, Sinutab 200mg tablets, Ibusor 200mg tablets, Austifen-200mg tablets, Betagesic 200mg tablets, Betaprofen 200mg tablets)	**18**	**1200**	**Oral**	**DD**	**M01AE01**	**Private**
2.Diclofenac (Adco-diclofenac 50mg tablets, Diclofenac 25mg Biotech tablets, K-fenak 50mg tablets, Mylan Diclofenac 50mg tablets, Diclofenac Sodium 50mg tablets, Panamor 25mg tablets)	**14**	**100**	**Oral**	**DD**	**M01AB05**	**Private**
3.Indomethacin (Mediflex 25mg capsules)	**1**	**100**	**Oral**	**DD**	**M01AB01**	**Private**
NASAL DECONGESTANTS						
1.Phenylephrine (Adco-naphensyl nose drops 100mg/10ml, Naphensyl nose drops 100mg/10ml)	**2**	**4**	**Nasal**	**DD**	**R01AA04**	**Private**
2.Pseudo-ephedrine (Sudafed sinus 60mg tablets)	**1**	**240**	**Oral**	**DD**	**R01BA02**	**Private**
MUCOLYTICS						
1.Acetylcysteine (ACC 200 200mg effervescent tablets, AMUCO 200mg effervescent tablets)	**3**	**1600**	**Inhalation**	**DD**	**R05CB01**	**Private**
2.Carbocisteine (Betaphlem	**4**	**1500**	**Oral**	**DD**	**R05CB03**	**Private**

250mg/5ml syrup, Bronchette 250mg/5ml syrup, Mucospect 250mg/5ml syrup)						
ANALGESICS/OPIOIDS						
1.Pholcodine (Pholtex forte 15mg/5ml syrup)	**13**	**50**	**Oral**	**DD**	**R05DA08**	**Private**
XANTHINES						
1.Theophylline (Adco-Alcophyllin 26.667mg syrup, Nuelin SA 250mg tablets, Theophen Bronchodilator 80mg/15ml syrup)	**12**	**400**	**Oral**	**DD**	**R03DA04**	**Private**
LEUKOTRIENE RECEPTOR ANTAGONISTS						
1.Montelukast (MONTE-AIR 10mg tablets, Topraz 10mg tablets)	**2**	**10**	**Oral**	**DD**	**R03DC03**	**Private**
SHORT-ACTING BETA AGONISTS						
1.Salbutamol tablets (Venteze 4mg tablets)	**5**	**12**	**Oral**	**DD**	**R03CC02**	**Private**
2.Inhaled Salbutamol (Asthavent 100mcg inhaler)	**2**	**0.8**	**Inhalation**	**DD**	**R03AC02**	**Private**
VITAMIN B COMPLEX PRODUCTS						
1.Vitamin B Complex (Zinplex B Complex tablets)	**5**	**Fixed dose**	**Oral**	**DD**	**A11EA**	**Private**
COMPLEMENTARY MEDICINES						
1.Cinnamon (Cinnamon complex)	**2**	**N/A**	**Oral**	**DD**	**N/A**	**Private**
VITAMINS						
1.Vitamin C (Clicks Vitamin C 500mg tablets)	**12**	**200**	**Oral**	**DD**	**A11GA01**	**Private**
IRON IN OTHER COMBINATIONS						
1.Complenatal FF capsules (Vitamins, Minerals, and Iron)	**1**	**Fixed dose**	**Oral**	**DD**	**B03AE02**	**Private**
MULTIVITAMINS						
1.Vital Multivitamin capsules (Multivitamin solution)	**2**	**Fixed dose**	**Oral**	**DD**	**R05X**	**Private**
PROKINETIC AGENTS/PROPULSIVES						
1.Metoclopramide (Adco-Contromet 10mg tablets)	**1**	**30**	**Oral**	**DD**	**A03FA01**	**Private**

OTHER COLD PREPARATIONS						
1.Glyco Thymol Co Mouthwash 100ml (Contains Glyco-thymoline and other ingredients)	**2**	**Fixed dose**	**Oral**	**DD**	**R05X**	**Private**
2.Dermadine oral gargle 100ml (Povidone-iodine 1g and other ingredients)	**1**	**Fixed dose**	**Oral**	**DD**	**R05X**	**Private**
3.Septo-cure throat spray 30ml (Contains an anaesthetic and an antiseptic)	**1**	**Fixed dose**	**Oral**	**DD**	**R05X**	**Private**
4. Aniline analgesic/ Nasal decongestant (Sinumax tablets – Paracetamol 500 mg/Pseudoephedrine 30 mg; Sudafed sinus pain tablets - Paracetamol 500 mg/Pseudoephedrine 60 mg; Sinustat capsules - Phenylpropanolamine hydrochloride 18 mg/Paracetamol 325mg)	**5**	**Fixed dose**	**Oral**	**DD**	**R01BA**	**Private**
5.Aniline analgesic/ NSAID (Ibupain capsules -Ibuprofen 200 mg/Paracetamol 250 mg)	**1**	**Fixed dose**	**Oral**	**DD**	**M01AE**	**Private**
6.Aniline analgesic/ Opioid (Spectrapain capsules – Paracetamol 320 mg/Codeine 8 mg; Adco-Napacod tablets -Paracetamol 500 mg/Codeine phosphate 10 mg; Codorol tablets - Paracetamol 500 mg/Codeine phosphate 8 mg; Cogesic tablets - Paracetamol 500 mg/Codeine phosphate 8 mg)	**11**	**Fixed dose**	**Oral**	**DD**	**N02BE**	**Private**
7.Antihistamine	**3**	**Fixed**	**Oral**	**DD**	**R06AX**	**Private**

/Nasal decong-estant (Actifed cold tablets - Pseudoephedrine 30 mg/5ml / Tripolidine 1.25 mg; Decofed tablets - Pseudoephedrine 30 mg/5ml / Tripolidine 1.25 mg; Demazin NS Repetabs - Pseudoephedrine 120 mg/Loratadine 5 mg)		**dose**				
8.Antihistamine /Xanthine (Alcophyllex syrup 100ml/200ml - Theophylline 16.667 mg/5ml / Diphenhydramine HCl 6.666 mg/5ml)	**49**	**Fixed dose**	**Oral**	**DD**	**R03DA**	**Private**
9.Antiseptic/Local anaesthetic (Cepacol Plus Original Lozenges - Cetylpyridinium chloride 1.399 mg/ Benzocaine 10 mg; Medi-Keel A Honey and Lemon Throat Lozenges - Cetylpyridinium chloride 1.5 mg/ Benzocaine 12 mg; Orochlor 100ml - Benzocaine 267 mg/100ml / Chlorhexidine 1mg/100ml)	**3**	**Fixed dose**	**Oral**	**DD**	**R02AD**	**Private**
10.Bronchodilator /Mucolytic (Flemeze Bronchodilatory syrup 100ml - Bromhexine Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml; Bisolvon Linctus DA 100ml - Bromhexine Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml; Bronkese Compound Linctus 100ml -	**3**	**Fixed dose**	**Oral**	**DD**	**R05CB**	**Private**

Bromhexine Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml; Adco-linctopent syrup 100ml/200ml - Bromhexine Hydrochloride 4 mg/5ml / Orciprenaline Sulphate 5 mg/5ml)						
11.Vitamin/Antiseptic/Antiseptic (Strepsils Orange-C Lozenges – Vitamin C 100 mg/Amylmetacresol 0.6 mg/2.4-Dichlorobenzyl Alcohol HSE 1.2 mg)	**2**	**Fixed dose**	**Oral**	**DD**	**R05X**	**Private**
12.Aniline analgesic/ Antihistamine/ Opioid (Famucaps - Paracetamol 300 mg/ Chlorpheniramine maleate 2 mg/ Phenylephrine HCL 5 mg)	**2**	**Fixed dose**	**Oral**	**DD**	**R01BA**	**Private**
13.Antiseptic/ NSAID (Andolex-C Lozenges Raspberry - Benzydamine hydrochloride 3 mg/Cetylpyridinium CL 1.33 mg; Andolex C Spray - Benzydamine hydrochloride 3 mg/Cetylpyridinium CL 1.33 mg)	**8**	**Fixed dose**	**Oral**	**DD**	**R02AD**	**Private**
14. Antihistamine /Expectorant /Nasal Decongestant (Sinuclear cough syrup - Pseudoephedrine HCI 30 mg/5ml / Triprolidine HCI 1.25 mg/5ml / Dextromethorphan Hydrobromide 10 mg/5ml)	**1**	**Fixed dose**	**Oral**	**DD**	**R06AX**	**Private**
15. Antihistamine	**1**	**Fixed**	**Oral**	**DD**	**R05FA**	**Private**

/Expectorant /Opioid (Trifen Expectorant Paediatric 100ml – Triprolidine 0.599mg/5ml / Guaifenesin 50mg/5ml / Codeine 3mg/5ml)		**dose**				
16.Opioid /Expectorant /Nasal Decongestant (Trifen Expectorant Adult 100ml - Pseudoephedrine 20mg/5ml / Guaifenesin 100 mg/5ml / Codeine 7.5 mg/5ml)	**1**	**Fixed dose**	**Oral**	**DD**	**R05FA**	**Private**
17. Opioid/Aniline analgesic/ NSAID (Ibupain forte capsules - Paracetamol 250 mg/Codeine 10 mg/Ibuprofen 200 mg; Mybucod tablets -Paracetamol 350 mg/Codeine 10 mg/Ibuprofen 200 mg; Mybulen capsules - Paracetamol 250 mg/Codeine 10 mg/Ibuprofen 200 mg; Myprodol tablets -Paracetamol 250 mg/Codeine 10 mg/Ibuprofen 200 mg)	**5**	**Fixed dose**	**Oral**	**DD**	**M01AE /N02BE**	**Private**
18.Opioid/Nasal Decongestant/ Antihistamine (Brunacod syrup 100ml – Codeine 9.199 mg/5ml / Promethazine HCl 3 mg/5ml / Ephedrine 7 mg/5ml)	**1**	**Fixed dose**	**Oral**	**DD**	**R05DA**	**Private**
19.Antihistamine/ Ammonium chloride/ Xanthine (Dilinct syrup 100/200ml - Etofylline nicotinate	**16**	**Fixed dose**	**Oral**	**DD**	**R06AA**	**Private**

105.5 mg/ Ammonium Chloride 410.5 mg/ Diphenhydramine 42.2 mg)						
20.Antihistamine/ Ammonium Chloride/ Sodium citrate (Bencough expectorant syrup 100ml - Ammonium chloride 136 mg/ Sodium citrate 65 mg/ Diphenhydramine 14 mg; Diphenhydramine expectorant syrup 100/200ml - Ammonium Chloride 137 mg/ Diphenhydramine 14.1 mg/ Sodium citrate 57mg; Phenorant syrup 100/200ml - Ammonium chloride 130 mg/5 ml / Sodium citrate 54.165mg/5ml / Diphenhydramine 13.33 mg/5ml; Relief-Coff EXP 100/200ml - Ammonium chloride 136 mg/5 ml / Sodium citrate 56 mg/5ml / Diphenhydramine 14 mg/5ml; Clear cough 100ml - Ammonium chloride 135 mg/5 ml / Sodium citrate 55 mg/5ml / Diphenhydramine 14.1 mg/5ml)	**74**	**Fixed dose**	**Oral**	**DD**	**R06AA**	**Private**
21.Vitamin/Nasal Decongestant/ Aniline Analgesic (Corenza Para-C Effervescent - Phenylephrine Hydrochloride 10 mg/ Paracetamol 650 mg/ Vitamin C 250	**1**	**Fixed dose**	**Oral**	**DD**	**R01BA**	**Private**

mg)						
22.Xanthine/ Aniline Analgesic/ Nasal Decongestant (Sinuend tablets - Caffeine 20 mg/ Paracetamol 200 mg/ Ephedrine 6 mg)	**5**	**Fixed dose**	**Oral**	**DD**	**R06AA**	**Private**
23. Xanthine/ Aniline Analgesic/ Nasal Decongestant/ Antihistamine (Flusin tablets - Caffeine 20 mg/ Paracetamol 200 mg/Pseudoephedrine 6 mg Chlorpheniramine 2 mg; Sinucon tablets - Caffeine 20 mg/ Paracetamol 200 mg/Pseudoephedrine 6 mg Chlorpheniramine 2 mg; Histacon capsules - Caffeine 30 mg/Paracetamol 200 mg/Phenylephrine 5 mg Chlorpheniramine 2 mg)	**25**	**Fixed dose**	**Oral**	**DD**	**R01BA**	**Private**
24. Xanthine/ Aniline Analgesic/ Opioid/ Antihistamine) (Acurate tablets – Paracetamol 450 mg/ Caffeine 30 mg/ Codeine phosphate 10 mg/ Doxylamine succinate 5 mg; Codoxol tablets - Paracetamol 450 mg/ Caffeine 30 mg/ Codeine phosphate 10 mg/ Doxylamine succinate 5 mg)	**6**	**Fixed dose**	**Oral**	**DD**	**N02BE**	**Private**
25. Ammonium chloride/ Sodium citrate/	**6**	**Fixed dose**	**Oral**	**DD**	**R06AA**	**Private**

Opioid/ Antihistamine (Phenorant with codeine syrup 100ml – Diphenhydramine 13.33 mg/5ml / Ammonium Chloride 130 mg/5ml / Codeine 8.33 mg/5ml / Sodium citrate 54.165 mg/5ml; Broncleer with codeine cough syrup 100ml - Diphenhydramine 12.5 mg/5ml / Ammonium Chloride 125 mg/5ml / Codeine 10 mg/5ml / Sodium citrate 50 mg/5ml)						
26.Ammonium Chloride/Sodium citrate/Antihistamine/Xanthine (Solphyllex syrup 100ml - Etofylline nicotinate 10 mg/30ml / Sodium citrate 300 mg/30ml / Ammonium Chloride 720 mg/30ml / Diphenylpyraline 8 mg/30ml / Theophylline 100 mg/30ml)	**10**	**Fixed dose**	**Oral**	**DD**	**R03DA**	**Private**
27. Xanthine/ Aniline Analgesic/ Opioid/ Carbamate (Adco-Salterpyn tablets - Caffeine Anhydrous 32 mg/ Meprobamate 150 mg/ Codeine phosphate 8 mg/ Paracetamol 320 mg; Stilpane tablets - Caffeine 32 mg/ Meprobamate 150 mg/ Codeine phosphate 8 mg/ Paracetamol 320 mg**)**	**32**	**Fixed dose**	**Oral**	**DD**	**N02BE**	**Private**
28.Vitamin/ Xanthine/ Aniline	**64**	**Fixed dose**	**Oral**	**DD**	**R01BA**	**Private**

analgesic/ Nasal decongestant (Flustat capsules - Ascorbic Acid 75 mg/Paracetamol 300 mg/Caffeine 30 mg/Chlorpheniramine maleate 2 mg/Phenylephrine HCL 5 mg)						
29.Antihistamine/ Xanthine/ Aniline analgesic/ Opioid (Tensopyn tablets -Doxylamine Succinate 5 mg/ Paracetamol 450 mg/ Caffeine 30 mg/ Codeine Phosphate 10 mg)	**7**	**Fixed dose**	**Oral**	**DD**	**N02BE**	**Private**
30.Antihistamine/ Oil derivative/ Ammonium chloride/ Sodium citrate/ Xanthine (Diatussin syrup 150ml – Diphenhydramine 28.149 mg/ Theophylline 56.31 mg/Ammonium Chloride 273.86 mg/ Sodium citrate 113.849 mg/ Menthol 2.279 mg)	**4**	**Fixed dose**	**Oral**	**DD**	**R06AA**	**Private**
31.Opioid/ Expectorant/ Ammonium Chloride (Benylin with codeine 100/200ml - Ammonium Chloride 125 mg/5ml / Codeine 10 mg/5ml / Diphenhydramine 12.5 mg/5ml)	**3**	**Fixed dose**	**Oral**	**DD**	**R05FA**	**Private**

Table O3: Dispensing patterns of medicines in the public sector

Drug name	Frequency	Defined Daily Dose (DDD) in mg	Route of drug admin-istration	Dispe-nser	ATC code	Sector
PENICILLINS						

1.Amoxicillin (Allmox 250mg capsules, Amoxicap 250mg capsules, Austell-amoxicillin 250mg capsules, Austell-amoxicillin 500mg capsules, Betamox 500mg capsules, Indo-amoxycillin 500mg capsules, Moxan 250mg capsules, Moxymax 250mg capsules, Moxymax 500mg capsules, Mymox 500mg capsules, Zoxil 500mg capsules)	**115**	**1500**	**Oral**	**Primary Healthcare (PHC) nurse**	**J01CA04**	**Public**
2.Phenoxy-methyl-Penicillin (Dezzpen 250mg tablets, Athlone Phenoxymethylpenicillin 250mg/5ML powder for injection)	**6**	**2000**	**Oral**	**PHC nurse**	**J01CE02**	**Public**
PENICILLIN/BETA LACTAMASE INHIBITOR COMBINATION						
1.Amoxicillin + Clavulanic acid (Austell-Co-amoxiclav 375mg suspension, Austell-Co-amoxiclav 625mg suspension)	**5**	**1500**	**Oral**	**PHC nurse**	**J01CR02**	**Public**
MACROLIDES						
1.Azithromycin (Austell azithromycin 500mg tablets, Cipla azithromycin 500mg tablets, Sandoz azithromycin 500mg tablets)	**12**	**300**	**Oral**	**PHC nurse**	**J01FA10**	**Public**
FLUOROQUINOLONES						
1.Ciprofloxacin (Biotech Ciprofloxacin 500mg tablets, Profloxin 500mg tablets)	**2**	**1000**	**Oral**	**PHC nurse**	**J01MA02**	**Public**
SULPHONAMIDE/FOLIC ACID INHIBITOR COMBINATIONS						
1.Sulfame-thoxazole/Tri-Methoprim (Nucotrim 400/80mg tablets)	**1**	**N/A**	**Oral**	**PHC nurse**	**J01EE01**	**Public**
CORTICOSTEROIDS						
1.Prednisone (Be-Tabs prednisone 5mg tablets)	**6**	**10**	**Oral**	**PHC nurse**	**H02AB07**	**Public**
ANTIHISTAMINES						
1.Chlorpheni-ramine (Allergex 4mg tablets,	**85**	**12**	**Oral**	**PHC nurse**	**R06AB02**	**Public**

Chlorpheniramine 4mg tablets)						
ANILINE ANALGESICS						
1.Paracetamol (Paracetamol 500mg tablets, Adco-napamol 500mg tablets, Austell-paracetamol 500mg tablets, Pacimol 500mg tablets)	**127**	**3000**	**Oral**	**PHC nurse**	**N02BE01**	**Public**
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)						
1.Ibuprofen (Ibusor 200mg tablets, Betagesic 200mg tablets)	**9**	**1200**	**Oral**	**PHC nurse**	**M01AE01**	**Public**
NASAL DECONGESTANTS						
1. Oxymetazoline (Iliadin nose drops 0.5mg/ml)	**9**	**0.4**	**Nasal**	**PHC nurse**	**R01AA05**	**Public**
SHORT-ACTING BETA AGONISTS						
1.Inhaled Salbutamol (Asthavent 100mcg inhaler)	**1**	**0.8**	**Inhalation**	**PHC nurse**	**R03AC02**	**Public**
VITAMIN B COMPLEX PRODUCTS						
1.Vitamin B Complex (Vitamino syrup 150ml, Zinplex Vitamin B Complex tablets)	**64**	**Fixed dose**	**Oral**	**PHC nurse**	**A11EA**	**Public**
VITAMINS						
1.Pyridoxine (Pyridoxine 25 mg tablets)	**1**	**160**	**Oral**	**PHC nurse**	**A11HA02**	**Public**
2.Folic acid (Gulf Folic acid 5 mg)	**1**	**0.4**	**Oral**	**PHC nurse**	**B03BB01**	**Public**
3.Thiamine (Thiamine 100 mg tablets)	**4**	**50**	**Oral**	**PHC nurse**	**A11DA01**	**Public**
OTHER COLD PREPARATIONS						
1.Glyco Thymol Co Mouthwash 100ml (Contains Glyco-thymoline and other ingredients)	**4**	**Fixed dose**	**Oral**	**PHC nurse**	**R05X**	**Public**
2.Antihistamine /Xanthine (Alcophyllex 100ml syrup - Theophylline 16.667 mg/5ml / Diphenhydramine HCl 6.666 mg/5m)	**1**	**Fixed dose**	**Oral**	**PHC nurse**	**R03DA**	**Public**
3.Vitamin/ Xanthine/ Aniline analgesic/ Nasal decongestant (Flustat capsules -	**1**	**Fixed dose**	**Oral**	**PHC nurse**	**R01BA**	**Public**

Ascorbic Acid 75 mg/Paracetamol 300 mg/Caffeine 30 mg/Chlorpheniramine maleate 2 mg/Phenylephrine HCL 5 mg)						

APPENDIX P: Drug-drug interactions in this study

Table P1: Drug-drug interactions between prescribed medicines in the private sector

Interacting pair of medicines	Sector/Healthcare Professional (HCP)	Explanation	Type	Frequency
Amoxicillin/Aspirin	Private/Non-dispensing doctor	Levels of one drug increased due to renal excretion	Moderate	1
Aspirin/Ascorbic acid	Private/Non-dispensing doctor	Levels of one drug increased due to renal excretion	Minor	1
Aspirin/Diclofenac	Private/Non-dispensing doctor	Levels of one drug increased due to renal excretion	Minor	1
Azithromycin/Amoxicillin	Private/Non-dispensing doctor	Antagonistic action	Minor	2
Azithromycin/Cetirizine	Private/Non-dispensing doctor	Levels of one drug increased due to absorption interactions	Moderate	3
Azithromycin/Pantothenic acid	Private/Non-dispensing doctor	Levels of one drug decreased due to absorption interactions	Moderate	6
Caffeine/Calcium gluconate	Private/Non-dispensing doctor	Levels of one drug decreased due to renal excretion	Minor	1
Chlorpheniramine/Caffeine	Private/Non-dispensing doctor	Antagonistic action	Moderate	2
Codeine/Caffeine	Private/Non-dispensing doctor	Antagonistic action	Moderate	4
Codeine/Chlorpheniramine	Private/Non-dispensing doctor	Increased sedation	Moderate	11
Diphenhydramine/Caffeine	Private/Non-dispensing doctor	Antagonistic action	Moderate	6
Diphenhydramine/Chlorpheniramine	Private/Non-dispensing doctor	Increased sedation	Moderate	18

Diphenhydramine /Codeine	Private/Non-dispensing doctor	Increased sedation	Moderate	12
Diphenhydramine /Loratadine	Private/Non-dispensing doctor	Increased sedation	Moderate	2
Diphenhydramine /Meprobamate	Private/Non-dispensing doctor	Increased sedation	Moderate	7
Diphenhydramine /Phenylephrine	Private/Non-dispensing doctor	Antagonistic action	Moderate	4
Diphenhydramine /Triprolidine	Private/Non-dispensing doctor	Increased sedation	Moderate	1
Doxylamine/Chlorpheniramine	Private/Non-dispensing doctor	Increased sedation	Moderate	3
Doxylamine/Diphenhydramine	Private/Non-dispensing doctor	Increased sedation	Moderate	2
Erythromycin/Caffeine	Private/Non-dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Minor	2
Erythromycin/Theophylline	Private/Non-dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Serious	5
Meprobamate/Chlorpheniramine	Private/Non-dispensing doctor	Increased sedation	Moderate	3
Moxifloxacin/Ibuprofen	Private/Non-dispensing doctor	Increased risk of toxicity	Moderate	1
Moxifloxacin/Prednisone	Private/Non-dispensing doctor	Increased risk of toxicity	Moderate	1
Phenylephrine/Doxylamine	Private/Non-dispensing doctor	Antagonistic action	Moderate	4
Prednisone/Diclofenac	Private/Non-dispensing doctor	Increased risk of toxicity	Moderate	2
Prednisone/Erythromycin	Private/Non-dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Serious	6
Prednisone/Ibuprofen	Private/Non-dispensing doctor	Increased risk of toxicity	Moderate	2
Sodium citrate/Aspirin	Private/Non-dispensing doctor	Levels of one drug increased due to renal excretion	Minor	1
Sodium citrate/Azithromycin	Private/Non-dispensing doctor	Levels of one drug decreased due to absorption interactions	Moderate	3

Theophylline/Prednisone	Private/Non-dispensing doctor	Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug	Moderate	11
Vitamin D/Calcium gluconate	Private/Non-dispensing doctor	Increased risk of toxicity	Moderate	1
Total				129

Table P2: Drug-drug interactions between dispensed medicines in the private sector

Interacting pair of medicines	**Sector/Healthcare Professional (HCP)**	**Type**	**Severity**	**Frequency**
Chlorpheniramine/Caffeine	Private/Dispensing doctor	Antagonistic action	Moderate	3
Chlorpheniramine/Pholcodine	Private/Dispensing doctor	Increased sedation	Moderate	1
Chlorpheniramine/Triprolidine	Private/Dispensing doctor	Increased sedation	Moderate	1
Ciprofloxacin/Caffeine	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Moderate	4
Ciprofloxacin/Theophylline	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Serious	4
Clarithromycin/Loratadine	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Serious	1
Clarithromycin/Prednisone	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Moderate - 5 Serious - 5	10
Clarithromycin/Theophylline	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Serious	3
Codeine/Caffeine	Private/Dispensing doctor	Antagonistic action	Moderate	4
Codeine/Chlorpheniramine	Private/Dispensing doctor	Increased sedation	Moderate	12
Codeine/Ephedrine	Private/Dispensing doctor	Antagonistic action	Moderate	2
Codeine/Meprobamate	Private/Dispensing doctor	Increased sedation	Moderate	1
Codeine/Pholcodine	Private/Dispensing doctor	Increased sedation	Moderate	1
Dexchlorpheniramine/Codeine	Private/Dispensing doctor	Increased sedation	Moderate	1
Dexchlorpheniramine/Ephedrine	Private/Dispensing doctor	Antagonistic action	Moderate	1
Diphenhydramine/Caffeine	Private/Dispensing doctor	Antagonistic action	Moderate	56

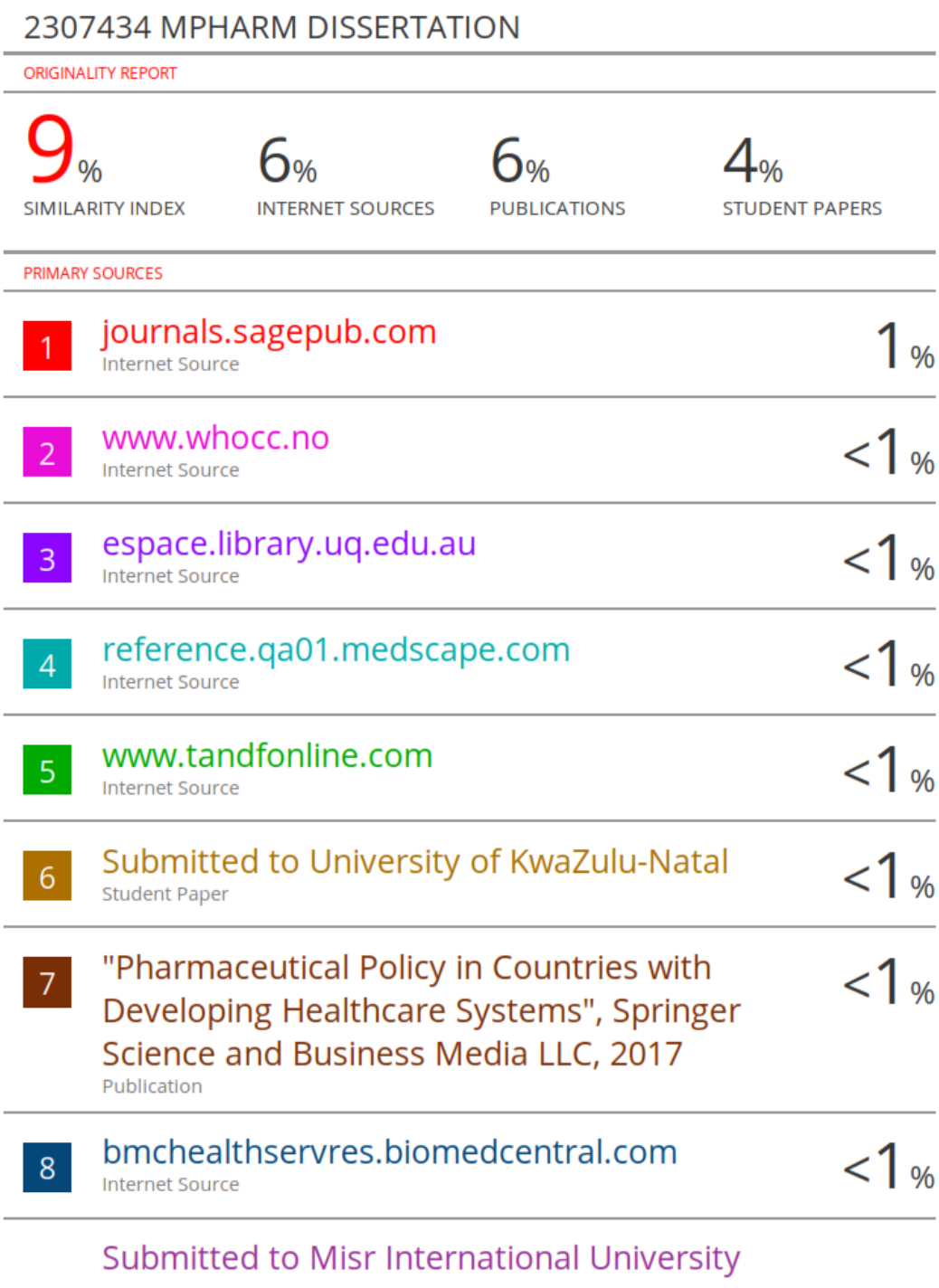
Diphenhydramine /Chlorpheniramin e	Private/Dispensi ng doctor	Increased sedation	Moderate - 18 Minor - 19	37
Diphenhydramine /Codeine	Private/Dispensi ng doctor	Increased sedation	Moderate	15
Diphenhydramine /Dexchlorpheniramine	Private/Dispensi ng doctor	Increased sedation	Moderate	2
Diphenhydramine /Ephedrine	Private/Dispensi ng doctor	Antagonistic action	Moderate	3
Diphenhydramine /Loratadine	Private/Dispensi ng doctor	Increased sedation	Moderate	2
Diphenhydramine /Meprobamate	Private/Dispensi ng doctor	Increased sedation	Moderate	10
Diphenhydramine /Phenylephrine	Private/Dispensi ng doctor	Antagonistic action	Moderate	44
Diphenhydramine /Triprolidine	Private/Dispensi ng doctor	Increased sedation	Moderate	1
Doxycycline/Amoxicillin	Private/Dispensi ng doctor	Antagonistic action	Serious	1
Doxycycline/Niacin	Private/Dispensi ng doctor	Levels of one drug decreased due to absorption interactions	Minor	1
Doxycycline/Pantothenic acid	Private/Dispensi ng doctor	Levels of one drug decreased due to absorption interactions	Minor	1
Doxycycline/Pyridoxine	Private/Dispensi ng doctor	Levels of one drug decreased due to absorption interactions	Minor	1
Doxycycline/Thiamine	Private/Dispensi ng doctor	Levels of one drug decreased due to absorption interactions	Minor	1
Doxylamine/Chlorpheniramine	Private/Dispensi ng doctor	Increased sedation	Moderate	3
Doxylamine/Diphenhydramine	Private/Dispensi ng doctor	Increased sedation	Moderate	2
Doxylamine/Ephedrine	Private/Dispensi ng doctor	Antagonistic action-	Moderate	1
Erythromycin/Caffeine	Private/Dispensi ng doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Minor	1
Erythromycin/Sodium citrate	Private/Dispensi ng doctor	Levels of one drug increased by the other drug directly	Moderate	1
Erythromycin/Theophylline	Private/Dispensi ng doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Serious	2
Meprobamate/Chlorpheniramine	Private/Dispensi ng doctor	Increased sedation	Moderate	4
Meprobamate/Ephedrine	Private/Dispensi ng doctor	Antagonistic action	Moderate	1
Meprobamate/Phenylephrine	Private/Dispensi ng doctor	Antagonistic action	Moderate	9
Meprobamate/Triprolidine	Private/Dispensi ng doctor	Increased sedation	Moderate	1
Metronidazole/Acetaminophen	Private/Dispensi ng doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Minor	1

Metronidazole/Theophylline	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Moderate	1
Phenylephrine/Caffeine	Private/Dispensing doctor	Decreased sedation	Moderate	1
Phenylephrine/Codeine	Private/Dispensing doctor	Antagonistic action	Moderate	10
Phenylephrine/Doxylamine	Private/Dispensing doctor	Antagonistic action	Moderate	1
Phenylephrine/Pseudoephedrine	Private/Dispensing doctor	Increased sympathetic (adrenergic) effects	Moderate	1
Prednisone/Ciprofloxacin	Private/Dispensing doctor	Increased risk of toxicity	Moderate	4
Prednisone/Diclofenac	Private/Dispensing doctor	Increased risk of toxicity	Moderate	5
Prednisone/Erythromycin	Private/Dispensing doctor	Levels of one drug increased due to metabolic enzymes with increased effects of the drug	Serious	1
Prednisone/Ibuprofen	Private/Dispensing doctor	Increased risk of toxicity	Moderate	5
Promethazine/Dexchlorpheniramine	Private/Dispensing doctor	Increased sedation	Moderate	1
Pseudoephedrine/Ammonium chloride	Private/Dispensing doctor	Levels/effects of one drug decreased by the other drug directly	Moderate	3
Sodium citrate/Ciprofloxacin	Private/Dispensing doctor	Levels of one drug decreased due to absorption interactions	Moderate	1
Sodium citrate/Doxycycline	Private/Dispensing doctor	Levels of one drug decreased due to absorption interactions	Moderate	3
Sodium citrate/Ephedrine	Private/Dispensing doctor	Levels of one drug increased due to renal excretion	Moderate	2
Sodium citrate/Pseudoephedrine	Private/Dispensing doctor	Levels of one drug increased due to renal excretion	Moderate	5
Theophylline/Cetirizine	Private/Dispensing doctor	Levels of one drug increased due to renal excretion	Minor	1
Theophylline/Prednisone	Private/Dispensing doctor	Levels of one drug decreased due to metabolic enzymes with decreased effects of the drug	Moderate	41
Triprolidine/Caffeine	Private/Dispensing doctor	Antagonistic action	Moderate	2
Triprolidine/Codeine	Private/Dispensing doctor	Increased sedation	Moderate	2
Triprolidine/Phenylephrine	Private/Dispensing doctor	Antagonistic action	Moderate	1
Total				341

Table P3: Drug-drug interactions between dispensed medicines in the public sector

Interacting pair of medicines	Sector/Healthcare Professional (HCP)	Type	Severity	Frequency
Azithromycin/Amoxicillin	Public/PHC nurse	Antagonistic action	Minor	1
Azithromycin/Pyridoxine	Public/PHC nurse	Levels of one drug decreased due to absorption interactions	Moderate	6
Azithromycin/Thiamine	Public/PHC nurse	Levels of one drug decreased due to absorption interactions	Moderate	5
Caffeine/Thiamine	Public/PHC nurse	Levels of one drug decreased due to absorption interactions	Minor	3
Ciprofloxacin/Pyridoxine	Public/PHC nurse	Levels of one drug decreased due to absorption interactions	Minor	4
Ciprofloxacin/Thiamine	Public/PHC nurse	Levels of one drug decreased due to absorption interactions	Minor	4
Diphenhydramine/ Chlorpheniramine	Public/PHC nurse	Increased sedation	Moderate	1
Prednisone/Ibuprofen	Public/PHC nurse	Increased risk of toxicity	Moderate	1
Theophylline/Pyridoxine	Public/PHC nurse	Levels of one drug decreased by the other drug directly	Minor	2
Total				27

APPENDIX Q: Turn it in report



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