Prescribing patterns of asthma treatment in the private healthcare sector of South Africa

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We are what we repeatedly do. Excellence then, is not an act, but a habit.

-Aristotle

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ABSTRACT

Title: **Prescribing patterns of asthma treatment in the private healthcare sector of South Africa.**

Keywords: Asthma, South Africa, drug utilisation review, chronic obstructive pulmonary disease, prescribing patterns, prevalence, cost of medications.

Asthma is a chronic disease of the airways and affects many people regardless of their age, gender, race and socioeconomic status. Since asthma is recognised as one of the major causes of morbidity and mortality in people and especially in South Africa, the prescribing patterns, prevalence and medication cost of asthma in South Africa are saliently important and need to be investigated.

A non-experimental, quantitative retrospective drug utilisation review was conducted on medicine claims data of a pharmaceutical benefit management company in a section of the private health care sector of South Africa. The study period was divided into four annual time periods (1 January 2008 to 31 December 2008, 1 January 2009 to 31 December 2009, 1 January 2010 to 31 December 2010 and 1 January 2011 to 31 December 2011). The prescribing patterns and cost of asthma medication were investigated and stratified according to province, age and gender. Patients were included if the prescriptions which were provided by the health care practitioners matched the Chronic Disease List (CDL) of South Africa and the International Classification of Disease (ICD-10) coding for asthma and chronic obstructive pulmonary disease (COPD). Data analysis was conducted by means of the SAS 9.3® computer package. Asthma patients were divided according to different age groups (there were five different age groups for this study), gender and geographical areas of South Africa.

The study indicated a steady increase in the prevalence of asthma patients from 0.82% (n = 7949) in 2008 to 1.18% (n = 15 423) in 2009 and reached a minimum of 0.79% (n = 8554) in 2011. Analysis of the prevalence regarding geographical areas in South Africa suggested that Gauteng had the highest number [n = 17 696, (0.85%)] of asthma patients throughout the study period, followed by KwaZulu Natal [n = 8 628, 1.16%)] and the Western Cape [(n =

8513, 0.97%) ($p < 0.05$)]. The prevalence of asthma in female patients [0.89% (n = 26 588)] was higher than in their male counterparts [0.79% (n = 19 244)] ($p > 0.05$). The results showed that asthma was not as common chronic disease in children. The total number of asthma patients younger than 7 years represented 0.64% (n = 2 909). It was found that patients over 65 years of age showed the highest prevalence of the five age groups [1.94% (n = 13 403) ($p < 0.05$)].

The average number of asthma prescriptions per patient per year was 8.28 (95% CI, 8.16-8.40) and 5.15 (95% CI, 5.06-5.23) in 2008 and 2011, respectively. The number of asthma items per prescription varied from 1.55 (95% CI, 1.55-1.56) in 2008 to 1.40 (95% CI, 1.39-1.40) in 2011.

Medication from the MIMS® pharmacological group (anti-asthmatics and bronchodilators) was used to identify asthma medication. The top three asthma medication with the highest prevalence in the study period were the anti-inflammatory inhaler of fluticasone (n = 39 721) followed by the single item combination product of budesonide/ formoterol (n = 25 121) and salbutamol (n = 24 296). The influence of COPD on asthma treatment and the cost-implication thereof were investigated. Medication from the MIMS® pharmacological group (anti-asthmatics and bronchodilators) was used to identify COPD medication. This study also showed that COPD had an influence in the economic burden of the South African asthma population.

The cost of medication is responsible for the single largest direct cost involved in the economic burden of asthma. This study showed that asthma represented 0.88% of the direct medication cost in the study (excluding hospitalisation and indirect cost). The average cost per prescription and average cost per asthma item both increased throughout the study period.

The prescribing patterns for the different medication used in the treatment of asthma were investigated and recommendations for further research in this field of study were made.

OPSOMMING

Titel: **Voorskrifpatrone vir asmabehandeling in die privaatgesondheidsektor van Suid-Afrika.**

Sleutelwoorde: Asma, Suid-Afrika, medisyneverbruiksoorsig, kroniese obstruktiewe pulmonêre siekte, voorskrifpatrone, voorkoms, koste van medikasies.

Asma is ‘n kroniese siekte van die lugweë wat baie mense raak – ongeag hul ouderdom, geslag, ras of sosio-ekonomiese status. Aangesien asma beskou word as een van die hoofoorsake van morbiditeit en mortaliteit in mense en veral in Suid-Afrika, is die voorskrifpatrone, voorkoms en medisynekoste van asma in Suid-Afrika van groot belang en moet van nader ondersoek word.

‘n Nie-eksperimentele, kwalitatiewe retrospektiewe medisyneverbruiksoorsig is onderneem ten opsigte van data oor medikasie-eise in ‘n farmaseutiese voordelebestuursmaatskappy in ‘n gedeelte van die privaatgesondheidsorgsektor van Suid-Afrika. Die studieperiode is in vier jaarlange tydsgleuwe opgedeel (1 Januarie 2008 tot 31 Desember 2008, 1 Januarie 2009 tot 31 Desember 2009, 1 Januarie 2010 tot 31 Desember 2010 en 1 Januarie 2011 tot 31 Desember 2011). Die voorskrifpatrone en koste van asmamedikasie is ondersoek en gestratifiseer volgens provinsie, ouderdom en geslag. Pasiënte is ingesluit indien die voorskrifte wat deur die gesondheidsorgpraktisyns gegee is, ooreengekom het met die Kroniese Siektelys (KSL) van Suid-Afrika en met die Internasionale Klassifikasie van Siektes (*International Classification of Disease ICD-10*) se kodering vir asma en kroniese obstruktiewe pulmonêre siekte (KOPS). Data-analise is hanteer deur die gebruik van die SAS 9.3® -rekenaarpakket. Asmapasiënte is verdeel volgens verskillende ouderdomsgroepe (altesaam vyf verskillende ouderdomsgroepe is vir hierdie studie gebruik), geslag en geografiese gebiede van Suid-Afrika.

Die studie het ‘n bestendige toename in die voorkoms van asmapasiënte vanaf 0.82% (n = 7949) in 2008 tot 1.18% (n = 15 423) in 2009 getoon, wat ‘n minimum van 0.79% (n = 8554) bereik het in 2011. Die analise van die voorkoms ten opsigte van geografiese gebiede in Suid-Afrika het getoon dat Gauteng die grootste aantal [n = 17 696, (0.85%)] asmapasiënte gehad het ten tyde van die studie, gevolg deur KwaZulu-Natal [n = 8 628, 1.16%)] en die

Wes-Kaap [(n = 8513, 0.97%) (p < 0.05)]. Die voorkoms van asma by vroulike pasiënte [0.89% (n = 26 588)] was groter as by hul manlike eweknieë [0.79% (n = 19 244)] (p > 0.05). Die resultate het getoon dat asma nie 'n algemene kroniese siekte onder kinders is nie. Die totale aantal asmapasiënte jonger as 7 jaar het 0.64% (n = 2 909) van die populasie uitgemaak. Daar is bevind dat pasiënte ouer as 65 jaar die grootste voorkoms van die vyf ouderdomsgroepe getoon het [1.94% (n = 13 403) (p < 0.05)].

Die gemiddelde aantal asmavoorskrifte per pasiënt per jaar was 8.28 (95% CI, 8.16-8.40) en 5.15 (95% CI, 5.06-5.23) in 2008 en 2011, onderskeidelik. Die aantal asma-items per voorskrif varieer vanaf 1.55 (95% CI, 1.55-1.56) in 2008 tot 1.40 (95% CI, 1.39-1.40) in 2011.

Medikasie vanaf die MIMS® farmakologiese groep (anti-asmatiese produkte en brongodilators) is gebruik vir die identifikasie van asmamedikasie. Die top drie asmamedikasies met die grootste voorkoms tydens die studieperiode was die anti-inflammatoriese inhaleerder van flutikasoon (n = 39 721) gevolg deur die enkelitem-gekombineerde produk van budesonied/ formoterol (n = 25 121) en salbutamol (n = 24 296). Die effek van KOPS op asmabehandeling en die koste-implikasie daarvan is ondersoek. Medikasie van die MIMS® farmakologiese groep (anti-asmatiese medikasie en brongodilators) is gebruik om KOPS-medikasie te identifiseer. Die studie het verder bevind dat KOPS bydra tot die ekonomiese las van die Suid-Afrikaanse asmabevolking.

Die koste van medikasie is verantwoordelik vir die enkele grootste direkte koste ten opsigte van die ekonomiese las van asma. Hierdie studie het bevind dat asma 0.88% van die direkte medikasiekoste in die studie verteenwoordig het (benwens hospitalisasie en indirekte koste). Die gemiddelde koste per voorskrif en die gemiddelde koste per asma-item het beide opgegaan tydens die studieperiode.

Die voorskrifpatrone vir die verskillende medikasies wat gebruik word vir die behandeling van asma is ondersoek en voorstelle vir verdere navorsing in die veld is aan die hand gedoen.

TABLE OF CONTENTS

CHAPTER 2: THE ASPECTS OF ASTHMA AS A CHRONIC DISEASE AND THE COMPLICATIONS THEREOF

CHAPTER 3: EMPIRICAL STUDY

CHAPTER 4: RESULTS AND DISCUSSION

CHAPTER 5: CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

LIST OF ABBREVIATIONS

AG	-	Age group (AG, AG2, AG3, AG4 and AG5)
AIDS	-	Acquired Immunodeficiency Syndrome
ANOVA	-	An Analysis of Variance
BDP	-	Beclomethasone
CDL	-	Chronic Disease List
CI	-	Confidence Interval
COPD	-	Chronic Obstructive Pulmonary Disease
COX	-	Cyclo-Oxygenise
CPI	-	Cost-prevalence index
DUR	-	Drug Utilization Review
ECRHS	-	European Community Respiratory Health Survey
EDL	-	Essential Drug List
EPR3	-	Expert Panel Report 3
FEV_1	-	Forced Expiratory Volume in One Second
GARD	-	Global Alliance against Respiratory Diseases
GORD	-	Gastro-Oesophageal Reflux Disease
GINA	-	Global Initiative for Asthma
GWAS	-	Genome Wide Association Studies
HIV	-	Human Immunodeficiency Virus
ICD-10	-	International Classification of Disease
ICS	-	Inhaled corticosteroids

IgE	-	Immunoglobulin E
IL13	-	Interleukin 13
IL33	-	Interleukin 33
IL1RL1	-	Interleukin 1 Receptor-like 1 Isoform 1
ISAAC	-	International Study of Asthma and Allergies in Childhood
LABA	-	Long acting β_2-agonists
LTRA	-	Leukotriene Receptor Antagonists
MDI	-	Metered Dosage Inhaler
MIMS®	-	Monthly Index of Medical specialities
MRC	-	South African Medical Research Council
NAEPP	-	National Asthma Education and Prevention Program
NAPPI	-	National Approved Product Pricing Index
NHLBI	-	National Heart, Lung and Blood Institute
NO_2	-	Nitrogen Dioxide
NSAIDs	-	Non–Steroidal Anti–Inflammatory Drugs
O_3	-	Ozone
OSA	-	Obstructive Sleep Apnoea
PBM	-	Pharmaceutical Benefit Management
PEF	-	Peak Expiratory Flow
PRACTALL	-	PRACtical ALLergy
PRN	-	As needed
QTc	-	QT corrected for heart rate
SABAs	-	Short-acting β_2-agonists
SAS 9.3®	-	Statistical Analysis System version 9.3

SD	-	Standard Deviation
SO_2	-	Sulphur Dioxide
SR	-	Stained Release
TSLP	-	Thymic Stromal Lymphopoietin
WHO	-	World Health Organization
χ^2	-	The Chi-square

LIST OF EQUATIONS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION AND OBJECTIVES

1.1 INTRODUCTION

This dissertation focuses on identifying the prescribing patterns of asthma therapy and treatment in a portion of the private health care sector of the South African population. These prescribing patterns will be identified and classified according to the medicine claim database. Data will be obtained from a South African pharmaceutical benefit management (PBM) company from the years 2008 to 2011. Obtained data will be used to investigate the identified prescribing patterns and the cost of asthma in a portion of the private health care sector of South Africa. Asthma treatment, treatment guidelines, risk factors, co-morbidities associated with asthma and other important issues surrounding the disease will also be discussed. Research questions that are applicable and important to this study have been formulated. Concomitantly, general and specific objectives for the current study have been set and the research methodology is discussed shortly. The divisions of chapters in the dissertation are also set out.

1.2 ASTHMA: AN OVERVIEW

Asthma is a clinical syndrome of unknown etiology that is characterised by episodes of breathing obstruction, airway hyper-responsiveness and a chronic inflammatory process of the airways of which mast cells, eosinophils, T-lymphocytes, epithelial cells and airway smooth muscle cells play a prominent role (Weiss *et al*., 2006:312; Gaga *et al.,* 2007:1049). Further studies have shown that genetic factors also play an in important role in asthma attacks (Bush & Zar, 2011:115). The chronic inflammation associated with asthma is linked to airway hyper-responsiveness that leads to symptoms of breathlessness, wheezing, coughing and chest tightness. These symptoms usually occur at night or early in the morning (Bateman *et al*., 2008:143; Bush & Zar, 2011:115). There are a number of factors that influence a person's risk of developing asthma. These factors can be divided into two categories, namely host factors (e.g. genetic, gender, obesity and hormonal fluctuations) and environmental factors (e.g. allergens, infections, tobacco and air pollution) (Gaga *et al*., 2007:1050; Bateman *et al.,* 2008:155).

In order to classify and measure the severity of asthma, the World Health Organisation (WHO) makes use of peak expiratory flow (PEF) or forced expiratory volume in the first second (FEV_1), symptoms, exacerbations and nocturnal symptoms. Asthma can be classified into four groups of increasing severity, namely intermittent, mild persistent, moderate, and severe, each with different treatment regimes (Bush & Zar, 2011:117). The most important and widely used asthma medication is β-agonists, leukotriene antagonists, methylxanthines and corticosteroids (Weiss *et al.,* 2006:314).

The first asthma guidelines were published in the mid 1980's when asthma became a major health problem in the world. The Global Initiative on Asthma (GINA) was launched in 1995 in association with the National Heart, Lung and Blood Institute (NHLBI) and the WHO to better understand asthma (Bousquet *et al.,* 2007:102). In spite of efforts to improve asthma therapy over the past decade, many patients have not benefited from these advances because of implementation failures of these guidelines.

Various co-morbidities are associated with asthma which can include one or more of the following: anxiety disorders, depression, OSA, GORD, migraine, rhinitis, chronic sinusitis and COPD (Boulet & Boulay, 2011:377). These co-morbidities complicate the treatment of asthma and also affect the health care costs for a patient. COPD is one of the most common co-morbidities associated with asthma (Boulet & Boulay, 2011:378).

1.3 PROBLEM STATEMENT

Asthma is a chronic inflammatory disorder of the airways and is regarded as one of the major causes of morbidity and mortality in people of all ages throughout the world (Gaga *et al.,* 2007:1050). Asthma affects approximately 300 million individuals worldwide and remains a major global health problem; indeed, the annual deaths from asthma have been estimated at 250 000 worldwide (Weiss *et al.,* 2006:312). In the United States of America, US$13 billion is spent on treatment of asthma, not counting the cost of lost workdays of asthmatics and the loss of lifetime earnings because of asthma mortality (Brandt *et al.,* 2012:2245).

There is a great deal of fear and uncertainty surrounding asthma and more resources should be invested into the management and education of asthma patients in South Africa (Green, 2001:346). Unlike tuberculosis that is more typically encountered in rural communities, asthma affects people from all backgrounds of life (Green *et al.,* 2008:212). It is a disease with no selectivity and people from different social, cultural and ethnic backgrounds can be diagnosed with asthma (Green *et al.,* 2008:212). Therefore, no matter where in South Africa

a healthcare giver is situated, he or she will at some point be in direct contact with asthma patients (Green *et al.,* 2008:212).

Chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease represent a major disease burden in low and middle income countries such as South Africa (Masoli *et al.,* 2004:472). Several treatments are available; also, avoiding risk factors like tobacco smoking and viral infections are known to control and slow the progression of the disease. However, little information is available on the health effects and cost associated with the population in South Africa (Stanciole *et al.,* 2012:2).

Worldwide, the prevalence of asthma tends to vary between 1% and 18% (Bateman *et al.,* 2008:145). According to the 2011 mid-year estimates from Statistics South Africa, the country's population stands at 50.5-million (StatsSA, 2011), which means that between 50 0000 and 900 0000 South Africans are at risk of developing asthma. According to Mash and colleagues (2009:892), asthma is the eighth leading contributor to the burden of diseases in South Africa. Some areas of South Africa have a high prevalence; as many as 1 in 10 people have asthma (Green *et al.,* 2008:212) and together with this incidence, among the highest mortality in the world with similar first world problems in regard with morbidity and cost. However, the cost of not treating asthma is even direr (Bateman *et al.,* 2008:145).

Thus, there is an urgent need to understand the complexities of asthma in this country and to determine the effect that it has on the population and economy of South Africa.

1.4 RESEARCH QUESTIONS

The following research questions can be formulated based on the foregoing discussion:

- What is asthma?
- What does drug utilisation review entail?
- What is the treatment cost of asthma in South-Africa?
- What is the prevalence of asthma in different age groups, geographical settings and gender?
- What do the prescribing patterns of asthma medication in South Africa entail?

- How many different asthma products are available in South Africa, and how are these classified?
- What is the influence of generic substitution on the cost of asthma treatment in South Africa?
- What is the influence of COPD on the cost of asthma treatment in South Africa?
- What asthma drug is most commonly used in South Africa?
- Which recommendations may be formulated regarding the usage of asthma therapy?

1.5 RESEARCH OBJECTIVES

The research objectives of this study can be divided into general research objectives and specific research objectives; these are discussed below:

1.5.1 General research objectives

The general and overall research objective of this study was to determine and review the prescribing patterns and cost of asthma therapy and treatment in a portion of the private health sector of South Africa. This main objective of this current study will be achieved by using information supplied by a medicine claims database of South Africa.

1.5.2 Specific research objectives

The specific research objectives that can be derived from the literature are:

- To review asthma severity as an illness with prevalence, risk factors and the treatment guidelines thereof, and
- To review asthma comorbidities, especially with COPD and its economic burden thereof.

These specific research objectives will be addressed in the literature overview presented in Chapter 2. The specific research objectives that will be answered in the empirical study include the following:

- To determine the prevalence of asthma from the year 2008 to 2011 stratified by age group, gender and geographical distribution in a section of the private healthcare sector of South Africa,
- To investigate the influence of gender and age on the prescribing patterns of asthma prescriptions and items according to the database and the cost-implication thereof, and
- To determine the medicine costs of treating asthma from the year 2008 to 2011 and the influence of age groups, gender and the cost incurred by the third-party payer as well as the patient (in form of levies),
- To determine the generic influence on asthma medication and the cost implication thereof and
- To investigate the prevalence of COPD in asthma patients and the cost-implication thereof.

1.6 RESEARCH METHOD

The methodological approach comprises two phases, namely a literature review and empirical investigation which are discussed below.

1.6.1 Phase one: Literature review

The literature review is divided into two steps:

Step 1: The discussion of asthma and the treatment thereof. A definition, diagnoses, pathogeneses and complications of asthma as a chronic disease are explored; and the guidelines for treating asthma are discussed.

Step 2: A reflection on the economic burden of asthma and asthma with COPDs in the South African population.

1.6.2 Phase two: Empirical investigation

This phase consists of six phases, namely:

- Selection of the research design.
- Selection of a study population.
- Selection of the measuring instruments.
- Data analyses.
- Report and discussion of the results of the empirical investigation.
- Recommendations based on the results of the empirical investigation.

A retrospective drug utilisation study will be conducted using data provided by the database of a pharmaceutical benefit management (PBM) company. The goal of a retrospective drug utilisation review is to identify and analyse prescribing patterns regarding the prescriptions for a specific disease (Lyles *et al.,* 2001:76). The study period stretches from 1 January 2008 to 31 December 2011. The criteria used in selecting the data of asthma and COPD were guided by the Chronic Disease List (CDL) of South Africa and the International Classification of Disease (ICD-10) coding. The ICD-10 coding for asthma is J45 to J46 while COPD patients are classified according to J44, as stated by the Council for Medical Schemes (refer to APPENDIX B). The CDL specifies 27 chronic conditions and their medication and treatment regime, and asthma and COPD are on this list.

The measurements on the database that are used include the following:

- Date of treatment.
- ICD-10 coding of asthma.
- Date of birth of the patient (to determine age groups).
- Gender.
- Postal codes of prescribers (to indicate geographical position).
- Indicator for generic products.
- Active ingredients.
- Cost of prescriptions and medicine items, which include the cost incurred by the third-party payer as well as the patient (in the form of levies).

1.6.2.1 Data source

Data has been obtained from a South African PBM company and is used to investigate the identified prescribing patterns of asthma in a section of the private health care sector of South Africa. Data analysis was done on an annual basis by using the Statistical Analysis System for Widows (SAS 9.3®) computer package.

1.6.2.2 The total database (total population) and asthma database (study population)

An asthma study population had to be extracted from the total database, also referred to as the total population. The total database contained the following information.

Table 1.1: General prescribing patterns of the total database for the years 2008 to 2011

Year	Total number of patients	Total number of prescriptions	Total number of medicine items	Total expenditure on medicine items (R)
2008	974 497	6 775 863	16 439 253	1 785 871 013.85
2009	1 307 528	9 023 205	21 648 991	2 509 210 769.88
2010	1 220 289	8 515 428	20 527 777	2 460 225 810.66
2011	1 077 834	7 371 213	17 766 594	2 010 783 076.00

The asthma study population was extracted from the total database (population). The total database contained a total number of 4 580 148 patients and asthma (n = 45 8320) represented 1.00% of all patinets on the database from 2008 to 2011.

Ethics approval was obtained from the North-West University Ethics Committee (NWU- 0005-07-A50.) The directors of the Pharmaceutical Benefit Management (PBM) company gave permission to perform this study.

1.7 DIVISION OF CHAPTERS

The chapter division of the dissertation can be set out thus:

Chapter 1: Introduction

Chapter 2: Aspects of asthma as a chronic disease and the complications thereof

Chapter 3: Empirical investigation

Chapter 4: Results and discussions

Chapter 5: Conclusions recommendations and limitations

1.8 CHAPTER SUMMARY

To conclude, this chapter served as an introduction to the rest of the dissertation. A short overview of asthma, including general facts, prevalence and co-morbidities associated with this condition were discussed. The research objectives and methodology were set out and discussed in brief. The division of chapters was also indicated. In Chapter 2 asthma as a disease and other important aspects associated with asthma are discussed in greater detail.

CHAPTER 2

THE ASPECTS OF ASTHMA AS A CHRONIC DISEASE AND THE COMPLICATIONS THEREOF

2.1 INTRODUCTION

Chapter 2 focuses on the definition and classification of asthma, its prevalence on a global scale, national and international asthma treatment guidelines, the risk factors associated with asthma, as well as the co-morbidities and the economic burden of asthma especially with COPD. The management and treatment of asthma have made huge strides over the recent years; however, many questions remain and many mysteries are yet to be solved. These previously mentioned factors play a crucial role, not only in the lives of patients, but also their families and in the broader South African society.

2.2 DEFINITION AND THE CLASSIFICATION OF ASTHMA

2.2.1 History

Asthma is a disease as old as time itself. In the 1870's the Egyptian Ebers Papyrus found hieroglyphics dating back to 1550 BC containing recipes that included a mixture of herbs heated on a brick so that the patients suffering from asthma could inhale these fumes and treat their symptoms (Myers & Tomasio, 2011:1390). Even the word asthma is derived from the Greek word *azein* which translates as "breathing hard" (Holgate, 2011:1340) and was first used in 450 BC by Hippocrates to describe a condition characterised by spasms of breathlessness (Haldar & Pavord, 2012:243).

It can, however, be said that our understanding of asthma has not advanced tremendously from these ancient times, until Hyde Salter described asthma as an intermittent, acute condition in his *Treatise on Asthma: Its Pathology and Treatment* in 1860 (Holgate, 2011:1339). In 1892, Sir William Olser combined clinical observation, physiology and pathology to capture the principal elements of asthma (Holgate, 2011:1339).

In the 1980's, asthma had only just become clearly understood as a potential serious disease among patients and the prevalence, morbidity and mortality of asthma were found to be increasing among all ages throughout the world (Bousquet *et al.,* 2007:102). In 1989, the Global Initiative for Asthma (GINA) programme was founded with a view to raise global awareness among public health and government officials, health care workers and the general public of the issue of asthma's prevalence being on the rise worldwide (Myers, 2008:755). While an incremental increase in morbidity and mortality in the 1980's characterised asthma in the United States, these trends peaked and reach a plateau in the 1990's (Myers & Tomasio., 2011:1390). In 1993, the GINA programme was implemented in order to develop a network of asthma patients in which individuals, organisations and public health officials could spread information regarding asthma care (Bateman *et al.,* 2008:144). In 1995, a programme was developed by the National Heart Lung and Blood Institute (NHLBI) of the USA, the World Health Organization (WHO) and GINA for asthma patients. This collaboration between the NHLBI, WHO and GINA was known as the Global Strategy for asthma Management and Prevention (Bateman *et al.,* 2008:144).

Despite advances in research over many centuries – since ancient writings on asthma and also in more recent history – there are still many great mysteries and dozens of patient-specific nuances that need to be discovered (Myers & Tomasio, 2011:1390).

2.2.2 Definition and terminology

Almost all definitions of asthma emphasise the notion of variable airflow obstruction; definitions invariably also highlight inflammation as an essential part of the disease (Vianna *et al.,* 2007:1146). However, defining asthma as a concept has been controversial and confusing for most. It is controversial because most recent documents describe asthma as a disease entity or concept, while for the better part of 50 years this has been argued to be inappropriate (Hargreave & Nair, 2009:1652). Also, defining asthma is confusing in the sense that asthma has come to mean different things to different people (Hargreave & Nair, 2009:1652). Asthma classification is further complicated by the multidimensional nature of the disease itself (Haldar *et al.,* 2008:221). The definition of asthma has changed considerably since 1892 when it was described by Sir William Osler (Braman, 2006:4S). Currently, all definitions are *descriptive* and include asthma symptoms and their patterns as well as the underlying mechanism with varying levels of detail (Papadopoulos *et al.,* 2012:978).

The modern definition of asthma involves four cornerstones, namely inflammation, hyper-responsiveness, bronchoconstriction and symptoms that include recurrent episodes of wheezing, breathlessness chest tightness and coughing (Löwhagen, 2012:713; Lalloo *et al.,* 2007a:20). Asthma is a disorder that is defined by its clinical, physiological and pathological characteristics (Bateman *et al.,* 2008:145). Bateman and colleagues (2008:146) of GINA and the National Asthma Education and Prevention Programme (NAEPP, 2007:S99) further define asthma as:

> *a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible spontaneously or with treatment.*

The WHO defines asthma as disease branded by symptoms of breathlessness and wheezing. It affects all age groups and varies in severity and frequency (WHO, 2013b). Furthermore, the disease is due to the inflammation in the lungs – a condition that, in turn, affects the nerve endings in the airways; so that they become swollen and cause airways to narrow and reduce the airflow from the lungs (WHO, 2013b).

The American Thoracic Society and European Respiratory Society provide a clear summarised definition of asthma that states that asthma is a heterogeneous condition (Reddel *et al.,* 2009:60). Its natural history includes exacerbations against a background of chronic persistent inflammation and/or structural changes of the airways that may be associated with symptoms and reduced lung functions (Reddel *et al.,* 2009:60). Unlike other chronic diseases such as hypertension and diabetes mellitus, asthma has symptomatic traits in the early stages of the disease's development (Lalloo & Mclvor, 2006:474). Lötvall *et al*. (2011:355) define asthma as a common chronic and complex disorder of the airways which is characterised by variable recurring symptoms such as bronchial hyper-responsiveness, airflow obstruction and underlying inflammation. It is thus clear that asthma is understood as a complex disease with different levels of severity, a natural history, co-morbidities, and different treatment regimes.

In light of the above, a clear standardised definition of asthma is needed that will promote the effective identification and treatment of patients. These patients will also benefit from this standardised definition which will, in turn, lighten the burden of the disease on their families and a country's healthcare sector (Bousquet *et al.,* 2010:928).

2.2.3 Classification

In 1991, an asthma severity classification was developed by the NAEPP and the NHLBI with a view to the long-term management for asthma. It has since been revised by their expert panel report in 1997 and updated on selected published topics in 2002 and 2007 (NAEPP, 2007:S95).

According to Lencher and Saltoun (2004:S22) the NAEPP uses the following factors to classify asthma severity:

- Frequency of clinical symptoms, and
- Objective measurements of lung function

Patients are then further classified into four groups based on their measurement of forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) before therapy, as well as daytime and nocturnal symptoms. Over time, a patient may be reclassified into different asthma severity categories (Lencher & Saltoun 2004:S22). The classification of severity must be applied in the absence of asthma therapy, but this is not always possible (Yawn *et al.,* 2005:297).

Currently, the NAEPP grid which is used to classify asthma severity is the standard tool for assessing asthma severity in patients. Although not perfect, it provides a simple and easy way for healthcare providers to assess asthma severity (Kwok *et al.,* 2006:77). This classification is summarised in table 2.1.

Table: 2.1: Asthma classifications in adults and children [adapted from Bateman *et al*., 2008:147; Lalloo *et al*., 2007a:21.]

Clinical features	Symptoms	Night time symptoms	Lung function
Mild intermittent	Symptoms ≤ twice a week Asymptomatic and normal PEF between exacerbations Exacerbations brief (From a few hours to a couple of days) Intensity may differ	≤ twice a month	FEV_1 or PEF ≥ 80% predicted variability < 20%
Mild persistent	Symptoms > twice a week but < once a day	> twice a month	FEV_1 or PEF ≥ 80% predicted PEF variability 20 to 30 %
Moderate persistent	Daily symptoms Daily use of inhaled short-acting β2-agonist Exacerbations affect activity Exacerbations ≥ twice a week, may last for days	> once a week	FEV_1 or PEF > 60% to 80% predicted PEF variability 30%
Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	FEV_1 or PEF ≤ 60% predicted PEF variability > 30%

FEV_1 – Forced expiratory volume in 1 second
PEF – Peak expiratory flow

These classifications are currently recommended for the initial assessment of asthma severity only, and are in the process of being replaced by the concept of 'control' which is

more useful for healthcare workers to work with (Papadopoulos *et al.,* 2012:978). These will be further explained in table 2.2 that presents the levels of asthma control.

Table 2.2: Levels of asthma control (adapted from Lalloo *et al.,* 2007a:24).

Characteristics	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	≤ twice/week	> twice/week	Three or more features of partly controlled asthma in any week
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for/relievers/rescue treatment	≤ twice/week	> twice/week	
Lung function (PEF/FEV_1)	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	Once or more/year*	Once in any week**

* Any exacerbation should prompt review of maintenance treatment to ensure it is adequate.

** By definition, an exacerbation in any week makes that an uncontrolled asthma week.

This control-driven approach towards asthma management is based on the same concept that was used for other chronic diseases such as diabetes and hypertension (Green *et al.*, 2007:172). The asthma management prevention programme recommends an initial assessment of asthma control treatment in order to achieve control, and adjustment of therapy to maintain control (Green *et al.*, 2007:172). The level of asthma control guides the

healthcare professional in deciding to maintain or to adjust therapy for the patient, i.e. step up treatment if necessary or step down if possible (Motala *et al.,* 2009:901).

The following terminology is used in asthma management; a definition and explanation are given in order to arrive at a clear understanding of what will be referred to further in this study.

2.2.4 Severe asthma

Severe asthma accounts for a significant portion of asthma morbidity, mortality and the healthcare burden, despite only comprising a small percentage of the total asthma community (Chipps *et al.,* 2012:259).

According to Bousquet and co-workers (2010:932), severe asthma can be defined by the level of current clinical control and risk as *"uncontrolled asthma which can result in the risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)."*

Severe asthma is divided into three groups, each of which carries different public health messages and challenges. These three groups are:

- Untreated severe asthma,
- Difficult-to-treat severe asthma, and
- Treatment-resistant severe asthma.

The latter can be divided into the following:

- Asthma for which control is not reached despite the highest level of suggested treatment: noncompliant asthma and corticosteroid-resistant asthma; and
- Asthma for which control can be maintained only with the highest level of recommended treatment (Bousquet *et al.,* 2010:932).

Severe asthma diagnoses are based on both the daily treatment regime of the patient and/or the clinical features that are present (Gaga *et al.,* 2007:1049).

From the definition of severe asthma one can conclude that severe asthma is associated with lower health related quality of life, high care utilisation rates and considerable social and economic burden.

In South Africa, acute severe asthma was also formerly known as status asthmaticus and can be defined as severe asthma development because of repeated β_2 agonist drugs that are unresponsive. Acute severe asthma is also defined as a medical emergency that requires immediate recognition and treatment (Kling *et al.,* 2013:201). Another angle on severe asthma is that it is a type of near-fatal asthma that can be defined as severe asthma associated with respiratory arrests with or without awareness (Holley & Boots, 2009:259).

2.2.5 Exacerbations

In most asthma patients, the disease can be realistically well controlled with a simple regime of inhaled drugs. However, some patients suffer from asthma exacerbations resulting in morbidity and mortality. Usually, these exacerbations account for a substantial proportion of the total health care cost of asthma (Ten Brinke *et al.,* 2005:812).

Asthma attacks or exacerbations are episodes of progressive increase in shortness of breath, wheezing, cough, chest tightness or a combination of these symptoms (Urbano*,* 2008:46; Bousquet *et al.,* 2010:930). Exacerbations are an important cause of asthma morbidity and in its severest form have led to hospitalisation and, in a small minority, death (Haldar & Pavord, 2012:245).

There are a number of definitions of asthma that can be used as a summary of this section:

Acute asthma is defined as a progressive increase in shortness of breath, wheezing, cough or tightening of the chest and which does not respond to the usual bronchodilator of the patient (Lalloo *et al.,* 2012:191).

Mild asthma exacerbations are asthma attacks which are outside the normal of variation for an individual patient and are difficult to distinguish from transient loss of asthma control (Reddel *et al.,* 2009:64).

Moderate asthma exacerbations can be defined as at least one of the following reoccurring for at least two days without the need for systemic corticosteroids:

- Increasing asthma symptoms;
- Worsening lung function; and/or
- Increased rescue bronchodilator usage (Reddel *et al.,* 2009:64).

2.3 PREVALENCE OF ASTHMA: A GLOBAL MAP

The prevalence of asthma as a chronic disorder has increased considerably in recent decades; to the extent so that it has become one of the world's most common chronic disorders (Anandan *et al.,* 2010:152; El Ftouh *et al.,* 2009:S21). The reasons for this reported increase in asthma prevalence are very complex, and there is no simple answer or a unique hypothesis that health care workers can use to explain these increases of asthma in world population (Nicolaou *et al.,* 2005:1357).

It seems that the global prevalence of asthma patients ranges between 1% and 18% globally with a concerning increase in asthma prevalence in both children and adults (Bateman *et al.,* 2008:145). If the current prevalence continues it is estimated that there will be an additional 100 million asthma cases by 2025 (Bahadori *et al*., 2009:1). These global increases in asthma prevalence are quite frightening when one considers the large number of variations that exists among the asthma populations in terms of genetics, lifestyle and environmental exposures (Keller & Lowenstein, 2002:319).

In some studies it appears that asthma prevalence has peaked and has even begun to decline in Western countries, whilst low and middle income countries are now experiencing increases in the prevalence of asthma, so that they now seem to be heading towards the high prevalence situation that prevailed in developed countries (Pearce & Douwes, 2005:1019; Mallol *et al.,* 2013:73; Pearce & Douwes, 2012:S95).

2.3.1 Gender differences

According to Vink and co-workers (2009:489), asthma is more common in boys than in girls around puberty, but by adulthood a gender switch occurs, with female patients showing a higher prevalence than their male counterparts (Vink *et al.,* 2010:498; Thomsen *et al.,* 2010:626). Contrary to this, a more recent study by Leynaert and co-workers (2012:626) showed that there are no differences in asthma prevalence in men and women between the ages of 20 and 30 years (Leynaert *et al.,* 2012:626). However, after the age of 35 years, women had a 20% increased risk of asthma than men of the same age (Leynaert *et al.,* 2012:626). Because this change in the male/female ratio occurs during puberty, hormonal changes throughout this period of life have been thought to be a potential cause of asthma Postma, 2007:136; Vink *et al.,* 2010:498; Clark *et al.,* 2010:154). Several sex hormones have been identified to play a role in premenstrual worsening of asthma in female patients of

which oestrogens and progesterone seem to be the leading causes (Van den Berge *et al.,* 2009:1478).

Table 2.3 summarises the prevalence of asthma among adult populations in South Africa.

Table: 2.3: Prevalence of asthma in adult population of South Africa: A summary of studies as indicated by the literature.

Study (yr. published)	Population (n, age range)	Outcome measure	Prevalence %	
			Male	Female
Wicht *et al.* (1977)	Northern suburbs, Cape Town (507, 20–80 yrs.)	Asthma	7.7	11.9
Nriagu *et al.* (1999)	South-Central Durban (693, ≥ 17 yrs.)	Asthma	12	12
Ehrlich *et al.* (2005)	National sample 13 826 > 14 yrs.)	Asthma	3.7	3.8

From table 2.3 it emerges quite clearly that asthma has a slightly greater prevalence among the female population. The prevalence between genders as well as the effect of age in the asthma population will be further discussed in Chapter 4.

2.3.2 Age differences

Asthma affects individuals across the entire age spectrum, from children to adults, with different phenotypes for each (Tsai *et al.,* 2012:1252). Although asthma can occur at any age in a patient's life, most cases have their origins in childhood, with a gradual decrease in incidence after adolescence (Thomsen *et al.,* 2010:626). The recent increase in asthma prevalence worldwide has led to numerous studies (Beasley e*t al.,* 2000:470; Almqvist *et al.,* 2008:47; Subbarao *et al.,* 2009:181). There are two major international studies that have

collected data and increased our knowledge about asthma prevalence and risk factors worldwide, one among children (the International Study of Asthma and Allergies in Childhood (ISAAC) (Beasley *et al.,* 1998:1225-1232) and the other among young adults, namely the European Community Respiratory health survey (Burney *et al.,* 1994:954-960; Mahboub *et al.,* 2012:4).

Asthma is the most common chronic disease of children and places a significant burden on the healthcare and educational systems of a country (Wildhaber *et al.,* 2012:346). It is estimated that between 25% – 66% of childhood asthma cases continue into adulthood (Chipps, 2008:44). In a recent study by the ISAAC, the prevalence of asthma in children of ages 13 – 14 years was found to be 14.1% and in the 6 – 7 year age group it was 11.7% (Mallol *et al.,* 2013:41; Beasley *et al.,* 1998:1228).

On the other end of the age spectrum, older adult asthma patients are not studied as often, and data on older asthma adults is very scarce (Hanania *et al.,* 2011:S5). It is not the case that asthma is a rare disease among elderly patients, but it is under-diagnosed because of its atypical nature and co-morbidity with Chronic Obstructive Pulmonary Disease (COPD) (Bellia *et al.,* 2007:1175). The prevalence of asthma is the same among patients aged between 65 and 84 years and younger adults (Reed, 2006:547). Furthermore, children who lived through the asthma epidemic of the 1980's are growing older. These children will be aged 64 years and older by 2030 and will bring their asthma history to this era, which will most likely progressively increase the numbers of older patients with asthma (Gibson *et al.,* 2010:803).Given the significant gaps in information between age differences in the literature, the objective of this study will be to present a clinical investigation into the aged-related differences of asthma in South Africa.

Table 2.4 summarises the prevalence of asthma in children, and adolescent populations in South Africa.

Table: 2.4: Prevalence of reported asthma in children and adolescents around South Africa: A summary of studies as indicated by the literature.

Study (yr. published)	Population (n, age range)	Outcome measured	Prevalence (%)
Burr *et al.* (1994)	Southern suburbs Cape town (1180, 12 yrs.)	Asthma	11.5
Ehrlich *et al.* (1995)	Mitchell's Plain, Cape Town (1995, 6-10 yrs.)	Asthma	10.8
Nriagu *et al.* (1999)	South-central Durban (376, < 17 yrs.)	Asthma	10
Poyser *et al.* (2000)	Cape Town (5178, 13-14 yrs.)	Asthma	13.3
Obihara *et al*. (2005)	Low-income area, Cape Town (861, 6-14 yrs.)	Asthma	12.3
Green (2011)	Cape Town & Polokwane (13-14 yrs.)	Asthma	20.7 18

It is clear from the table that the prevalence of asthma in South Africa is very high; it is also on the increase in all populations over the last few decades (Green, 2011:9). Table 2.4 also indicates that most studies were conducted among young adolescents between 13-14 years old.

2.3.3 Asthma in Africa and South Africa

In sub-Sahara Africa, the high burden of opportunistic infectious diseases – particularly tuberculosis, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) and malaria – has meant that governments, research funders and researchers did not consider asthma as a health priority (Ait Khaled *et al.,* 2007:247). Asthma has, however, been increasing steadily over the past few decades in both developed and developing countries. Globally, about 300 million people have asthma, of which 50 million are in Africa (English *et al.,* 2007:224). South Africa's asthma prevalence is ranked 25th globally with a 8.1% prevalence of the population presenting with asthma symptoms (Masoli *et al.,* 2003:9)

In South Africa (specifically in Cape Town), the 12-month prevalence of wheezing, assessed using the ISAAC phase I and phase III questionnaires in 13- to 14-year-olds, was found to have increased from 16.0% to 20.3% over the period 1995 – 2002. However, no corresponding increases in the prevalence of clinician-diagnosed asthma over the same time period were noted (Anandan *et al.,* 2010:153).

These percentages of asthma prevalence are lower compared to more industrialised countries, except that South Africa shows the same rates as found in the United Kingdom (Wjst & Boakye, 2007:204). South Africa has high incidence of asthma prevalence and, more worrying, among the highest mortality rates in the world (Green, 2011:14). According to Masoli and co-workers (2003:12) South Africa mortality rate is ranked fourth (18.5 case fatality rate per 100 000 asthmatics) globally (Masoli et al., 2003:12). In Casablanca (Morocco), Grand Tunis (Tunisia), Nairobi (Kenya) and Cape Town (South Africa), asthma currently shows a higher prevalence in the urban than the rural areas (Ait Khaled *et al.,* 2007:257).

In African countries which are becoming more westernised, the prevalence of asthma is higher. Owning to the projected increase in urban population in sub-Sahara Africa, it is estimated that there may be an increase of at least 35% in the number of people with asthma by 2015 (Van Gemert *et al.,* 2011:241).

Africa provides a unique platform for many more developed countries to study the early stages of the transition to urbanised economics, providing opportunities to look for the risk factors of early sensitisation and later development of asthma (Broder *et al.,* 2002:809). It is for this reason that Africa probably has more to offer researchers in terms of the development in asthma than any other continent in the developed world (Wjst & Boakye, 2007:205).

2.3.4 Global map

The sharp increase of asthma prevalence over the last 40 years means that nearly 300 million people worldwide are suffering from the symptoms associated with this disease (WHO 2013a). The prevalence of asthma is estimated to increase by 50% every decade (Braman, 2006:S4). Since the 1990's, most studies on the prevalence of asthma and allergies had been conducted in English-speaking nations like Australia, the United Kingdom and New Zealand (Asher *et al.,* 2006:733). The prevalence of asthma varies amongst different countries, ranging from the lowest in China (0.2%) to the highest in Australia (21.0%) (To *et al.,* 2012:3). It has been suggested that approximately 35.5 million people inNorth America have asthma, which translates to 1 in every 10 people (Masoli *et al.,* 2003:86). For Central and South America, the prevalence suggests that there are more than 5.2 million asthma cases (Masoli *et al.,* 2003:92).

According to the WHO fact sheet, the scale of asthma as a worldwide problem has reached serious levels (WHO, 2013a):

- Around 8% of the Swiss population suffers from asthma as compared to 2% only 30 years ago;
- In the United States of America, the number of asthma patients has increased with 60%;
- Asthma in Western Europe has doubled in the last ten years;
- Japan has now a population of 3 million asthmatics.

Asthma also affects developing countries where the prevalence of the condition varies greatly:

- India has an estimated 15-20 million asthmatics;
- The prevalence of asthma in Kenya is nearly 20%;
- In the Western Pacific region of the WHO, the prevalence varies from over 50% among children in the Caroline Islands to virtually zero in Papua New Guinea.

To get a true perspective of the prevalence of asthma, figure 2.1 provides a global map adapted from Masoli *et al.* (2003:9) that shows the most affected areas in the world.

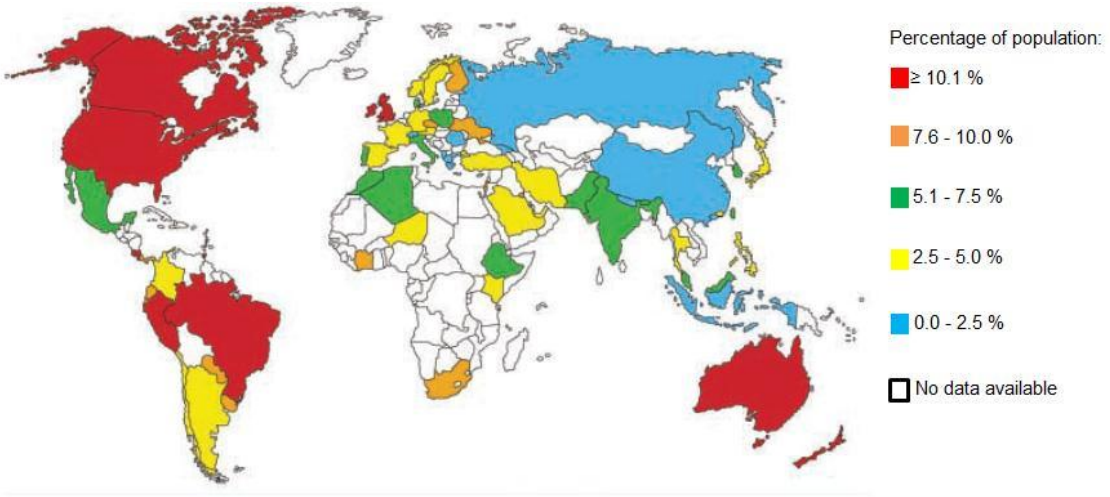


Figure 2.1: The worldwide prevalence of asthma, adapted from Masoli *et al.* (2004:472).

In short, the literature indicates a clear pattern: highly industrialised (developed) countries such as Australia and countries in Western Europe have a higher prevalence of asthma compared to middle-income countries, especially in eastern and central Europe (Sembajwe *et al.,* 2010:283). The strategies behind national and international comparisons of asthma prevalence are used to identify the causes of asthma and to get an improved understanding of asthma as a disease (Beasley *et al.,* 2000:467).

2.4 RISK FACTORS

Most patients suffering from asthma show atopic symptoms. It is only when these patients are exposed to certain stimuli that set inflammation into motion as well as structural changes in the airway, causing hyper-responsiveness of the airway and variable airflow obstruction, which in turn cause most asthma symptoms. There are many such stimuli and the most important ones include environmental allergens, occupational sensitising agents, and respiratory viral infections (Dennis *et al.,* 2008). Using the information associated with risk factors will help with asthma management since it will facilitate identifying new risk factors in young and old asthma patients, applying them in early intervention with available therapies, and conducting further studies to identify more effective strategies to alter the course of asthma itself. Risk factors that influence asthma can be divided into host factors and environmental factors.

2.4.1 Host factors

A host factor is a medical term referring to the traits of an individual person that affect susceptibility, exposure or response to a disease like asthma.

Heredity - In most asthma patients, symptoms appear before the age of six years (Martinez *et al.,* 1995:137). A child with two asthmatic parents has an 80% to 90% probability of developing asthma, and a 30% to 40% chance of developing asthma if only one parent is asthmatic (Duffy, 1997:130). Another risk factor is a family history of allergic rhinitis, which triples the chance of developing asthma (Cruz *et al.,* 2007:21).

Genetics – This is an exciting time in the field of asthma genetics. The publication of studies such as the Genome Wide Association Studies (GWAS) generates hope that this list will expand our understanding of the common and unique pathways of asthma (Ober & Yao, 2011:25). Over 200 genes have been identified in candidates and GWAS that determine the complexity of asthma as a disease, which include genes such interleukin 13 (IL13) and interleukin 33 (IL33), their receptor interleukin 1 receptor-like 1 isoform 1 (IL1RL1) and thymic stromal lymphopoietin (TSLP) (Postma, 2007:139; Ober & Yao, 2011:30; Apter, 2012:70). In a recent study by Thomsen *et al.* (2010:628) it was found that genetic factors contribute roughly towards one third of the onset of asthma. However, environmental factors also play an important role and account for two thirds of asthma onset (Thomsen *et al.,* 2010:628).

Hormonal disturbances – Asthma may worsen during the pre-menstrual period in up to 40% of females, possibly due to a reduced response to corticosteroids and bronchodilators. The higher prevalence of adult-onset asthma and severe asthma in females than in males suggests possible hormonal influence (Boulet, 2009:900).

Respiratory infections – Viral agents like the rhinoviruses are frequently detected in about 80% of children, and in 41% – 78% of adults (Boulet & Boulay, 2011:383; Papadopoulos *et al.,* 2011:460). These respiratory viral infections have also been strongly linked to asthma exacerbations in patients (Papadopoulos *et al.,* 2011:458). Other micro-organisms such as

atypical bacteria (which include *Chlamydophila pneumonia* and *Mycoplasma pneumonia*) may also be associated with asthma exacerbations (Papadopoulos *et al.,* 2011:463)

Obesity – As the rising trend of obesity engulfs the developed world, so does the list of diseases associated with being overweight lengthens. One of these diseases is asthma (Kent & Lane, 2012:213). Obese children and adults are found to be at a higher risk of developing asthma (Lang, 2012:70; Holguin *et al.,* 2011:1488). There is also evidence that obesity complicates asthma treatment by reducing the effects of asthma medication in asthmatic patients (Boulet, 2013:16).

Drugs – Shortly after aspirin therapy was introduced about 100 years ago, some patients reported episodes of bronchospasms after taking aspirin (Szczeklik & Stevenson, 2003:913). Aspirin and non–steroidal, anti–inflammatory drugs (NSAIDs) are among the most widely prescribed drugs in the world (Vane & Warner, 2000:1373; Vane & Botting, 2003:255). The cyclo-oxygenase (COX)-mechanism appears to be the key enzyme that can explain aspirin-sensitive asthma (Picado & Valero, 2001:179). The ability of NSAIDs to inhibit COX-2 may explain their anti-inflammatory effects on a patient, while the inhibition of COX-1 may account for their unwanted side effects, such as the aspirin-induced asthma (Vane & Botting, 2003:256). Aspirin-induced asthma affects approximately 10-15 % of asthmatics (Szczeklik & Stevenson, 2003:918).

Occupational exposure – Occupational asthma refers to asthma induced by exposure in the working environment to inhalation exposure, with or without pre-existing asthma (Cowl, 2011:674). Asthma-induced occupational exposure has been documented in developing countries. South Africa is no different; the country has an average annual incidence of asthma among 13.1 per million employed workers and asthma is the second most common occupational lung disease reported after pneumoconiosis (Esterhuizen *et al.,* 2001:509; Bousquet *et al.,* 2003:271). The most frequently reported agent is latex followed by isocyanates (a component of automotive spray paints and polyurethane foam products) and platinum salts (Lombardo & Balmes, 2000:698; Bousquet *et al.,* 2003:271). Treatment of occupational asthma often focuses on avoiding the trigger and, as a result, many patients may be unable to perform their workplace activities. However, there are compensation systems in place to protect the worker in such a case (Cowl, 2011:680).

2.4.2 Environmental Factors

Asthma has long been documented as a complex genetic disease that is mediated by exposure to a variety of environmental triggers (Miller & Ho, 2008:567). The prevalence of these environmental risk factors in asthma has been widely reported (Sterling 2012:144; Amato, 2011:29). Environmental factors are specific allergens that target the immunoglobulin E (IgE)-mediated immune response located on mast cells in the lungs which in turn causes inflammation and bronchoconstriction in patients (Peden & Reed, 2010:150).

Because adults and children tend to spend more time indoors, the potential for exposure to indoor environmental factors to affect asthma in patients has become more important than ever before (Eisner *et al.,* 2002:977). These environmental factors will likely be important in explaining regional differences and the overall increase of asthma's prevalence (Heinrich, 2011:1).

In order to properly manage asthma we require a clear understanding in environmental exposures, both indoors and outdoors (Diette *et al.,* 2008:602).

2.4.2.1 Indoor environmental factors

Asthma is a threatening disease to human health which involves long term treatment and high cost (Feng *et al.,* 2012:7). According to annual reports published by GINA, more than 50% of adults and 80% of children are sensitive to allergic factors. Indoor environmental exposures are a major risk factor in the increased prevalence of asthma (Bryant-Stephens, 2009:1201). Indoor allergens such as house dust mites, pet dander, cockroaches and mould are of particular importance (Gehring *et al.,* 2001:555).

The following will be classified under indoor allergens:

Pet allergens – Cats and dogs are common pets in most parts of the world, but these animals are associated with a high prevalence of allergic asthma (Jie *et al.,* 2011:559).

Dust mites – The dust mite allergen is not only a common indoor allergen, but is also one of the most important pathogens causing allergic asthma in many parts of the world (Hales *et al.,* 2006:362). In a recent study by El-Ghitany and Abd El-Salam (2012:383), evidenceshowed that there was a 66% chance of dust mite sensitivity in asthmatic children; these results were also confirmed by Shin *et al.* (2005:635).

Cockroach – Cockroach allergy is a widespread risk factor in South Africa (Motala *et al.,* 2011:10). The exposure to cockroach allergens is associated with wheezing and asthma morbidity (Sheehan *et al.,* 2010:579). Parental exposure to these allergens may also prime the foetus's immune system before birth, and may thus contribute to the development of allergic asthma (Sheehan *et al.,* 2010:579).

Mould – Moulds or microfuge that grow in dark damp areas and damp houses may contain a large number of mould spores (Arshad, 2010:50). Certain levels of *Alternaria alternate* (a common type of mould) have been associated with increased asthma morbidity (Diette *et al.,* 2008:610; Grimsley *et al.,* 2012:1605). A study by Jafta and colleagues (2012:1110) suggests that subtropical climates like Durban in Kwazulu-Natal encourage the growth of fungi. They also found that homes where the suggested risk threshold of airborne fungal concentrations are exceeded most likely housed children classified as asthmatic patients (Jafta *et al.,* 2012:1117).

Tobacco smoke – Smoking indoors refers to the involuntary or voluntary inhalation of tobacco smoke that contains particles and gases generated by the combustion of paper, additives and tobacco of cigarettes (CEPA, 2006:1). Tobacco exposure is one of the strongest known environmental exposures of the natural history of asthma at any age (Martinez *et al.,* 1995:137). Exposure to environmental tobacco smoke is common in both children and adults, and has been associated with a decrease in the lung function in asthma patients (Jie *et al.,* 2011:556; Carlsen & Carlsen, 2008:14). Reduced responsiveness to corticosteroids and leukotriene modifiers have also been noted in asthma patients who smoke, as compared to non–smokers (Lazarus *et al.,* 2007:175).

Currently, African countries like South Africa, Botswana and Mauritius have the same consumption rate of tobacco as those in developed countries (Bousquet *et al.,* 2003:273). However, increases in tobacco consumption are addressed by means of the following acts: In 1994 the first Tobacco Products Control Act was passed and as from 1999, South Africa became one of the first countries in the world to ban smoking in public places when it introduced its Tobacco Products Control Amendment Act (Steyn *et al.,* 2002:161). These acts put a serious dent in the smoking culture in South Africa, as it prohibited smoking in restaurants, pubs, shopping centres and offices where there was no separate or an enclosed smoking room. These acts also protect children and adolescents from marketing campaigns

by banning promotions and advertisements of tobacco products (Van Walbeek *et al.,* 2002:208).

Sensitisation to one or more of the common indoor environmental factors has been consistently associated with asthma and allergy among adults and children (Arshad, 2010:53).

2.4.2.2 Outdoor environmental factors

Most individuals have little control over outdoor environmental factors, and there are several of these factors that may have an influence on asthma. Well-known culprits here include the ozone (O_3), nitrogen dioxide (NO_2) and sulphur dioxide (SO_2) (Diette *et al.,* 2008:611). A growing number of studies show that patients living in close proximity of traffic have an increased risk of new-asthma onset, asthma exacerbations, asthma symptoms and asthma-related hospitalisations, especially among children (Gilliland, 2009:S168; D'Amato *et al.,* 2010:96).

Ozone - O_3 is generated at ground level by chemical reactions involving NO_2, hydrocarbons and UV light (D'Amato *et al.,* 2013:4). The danger associated with O_3 is that it can increase airway inflammation and hyper-responsiveness with an increased risk of asthma exacerbation in asthma patients (Bayram *et al.,* 2001:293).

Nitrogen dioxide - NO_2 is an air pollutant produced by the oxidisation of nitrogen oxide from industrialised factories. It is also produced during the combustion process of cars and truck engines (Takenoue *et al.,* 2012:762). Like O_3, NO_2 is an oxidant pollutant, although it is less chemically reactive (D'Amato *et al.,* 2013:4). In a case control study by Lindgren and co-workers (2010:12) it was found that living in a 50m radius of a road with high traffic (and therefore high NO_2 concentrations) can be associated with an increase in asthma prevalence and symptoms.

Sulphur dioxide – SO_2 is an ambient outdoor air pollutant that is mainly formed by the combustion of high-sulphur coal or oil (Diette *et al.,* 2008:612). The 2007 NAEPP suggests

that patients with asthma should avoid exercise outdoors if SO_2 concentrations are high (NAEPP, 2007, Diette et al., 2008:611).

Pollen allergens – Pollen and allergens are major outdoor allergens (Diette *et al.,* 2008:612). Pollen allergy is frequently used in studies to determine the interrelationshipbetween air pollution and allergic respiratory disease like rhinitis and asthma (D'Amato *et al.,* 2013:5). An important clinical feature of pollen allergy in South Africa is that grass pollen allergic symptoms occur for almost 10 months of a year, due to the long pollination seasons (Taborda-Barata & Potter, 2012:2).

Urbanisation – There are noticeable trends associated with rapid urbanisation and asthma in South Africa; it is clear that action should be taken before this tendency reaches more serious proportions (MacIntyre *et al.,* 2001:671). There are actually several factors that may explain why there is an expected rise in asthma prevalence between rural and urban areas, including obesity, heavy traffic volumes and a higher rate of smoking and concomitant smoke inhalation (Robinson *et al.,* 2011:1055).

Another interesting factor related to urbanisation is the hygiene hypothesis, which states that environmental changes in the industrialised world have led to reduced microbial exposure in childhood, which results in the increased prevalence of allergic sensitization and diseases like asthma (Platts-Mills *et al.,* 2005:25).

These differences in the prevalence of allergic diseases between urban and rural areas are a real factor in the understanding of asthma, but these patterns vary across various phenotypes, and different causes may be responsible for these observed differences (Nicolaou *et al.,* 2005:1359).

It seems clear from the above discussion that there is no single factor that can be held responsible for the onset of asthma, and that the condition is thus clearly a multi-factorial in aetiology (Green, 2011:10). Although the associations between air pollution and respiratory asthma are complex, there are opportunities to improve the environment for the sake of asthma patient's health (Diette *et al.,* 2008:612).

2.5 GUIDELINES FOR TREATING ASTHMA

A number of asthma guidelines have been developed over the past 20 years with a view to developed to promote international collaboration in asthma research and development, increase the awareness of asthma among health professionals, to evaluate published reports on asthma and to improve asthma management (Potter, 2010:1). Most industrialised countries such as the United States, Canada, the United Kingdom, Australia and New Zealand have developed their own asthma management guidelines (Lalloo & Mclvor, 2006:480). The first international guidelines for managing asthma were published in 1992, and GINA was launched in 1993 by the WHO (IPCRG, 2008). The availability of national and international guidelines provides health care workers with evidence-based recommendations and management guidelines for asthma (Tomlins, 2006:71).

There are currently four major propagators of guidelines that address the management of asthma, namely:

2.5.1 The Expert Report Panel (EPR-3) of the NAEPP;

2.5.2 The Practical Allergy (PRACTALL) Consensus Report published by the European Academy of Asthma and Allergy in 2008;

2.5.3 The International Primary Care Respiratory Group (IPCRG) Guidelines on the management of chronic respiratory diseases in primary care, and

2.5.4 GINA (which has published new evidence based guidelines for the diagnoses and management of asthma).

These four guidelines will be discussed and summarised shortly.

2.5.1 The EPR3 of the NAEPP

In 1989, the NHLBI established the NAEPP with a view to begin the process of developing consensus on science-based guidelines for the diagnosis and management of asthma (Myers, 2008:755). The first of the NAEPP guidelines for the management of asthma were published in 1991, and updates were made in 1997 and 2002 and in 2007 (NAEPP, 2007:S95). The EPR-3 guidelines are comprehensive documents that discuss the definition, pathophysiology, and pathogenesis of asthma; the long-term management of asthma; the management of asthma in special populations; and the management of asthma exacerbations (Urbano, 2008:42). These guidelines contain three tables that can be used to assess and

manage asthma severity in children aged 0-4 years, 5-11 years and ≥ 12 years (NAEPP, 2007:S96). The stepwise approach for the management of asthma in adults and children younger than five years adapted from (NAEPP, 2007:S97) can be seen in table 2.5.

Table 2.5: The stepwise approach for managing acute or chronic asthma in children younger than five years (NAEPP, 2007:97)

Classify Severity: Clinical Features before treatment or Adequate Control					Medications Required to maintain Long term Control
	Symptoms		PEV or FEV_1 (%) of prediction	PEF Variability (%)	Daily Medications
	Day	Night			
Severe persistent	Continual	Frequent	≤ 60	> 30	**Preferred Treatment**: High-dose inhaled corticosteroids and long-acting inhaled β_2 agonistsIf needed, corticosteroid tablets or syrup long-term.
Moderate persistent	Daily	> 1 night/weak	> 60-< 80	> 30	**Preferred treatment:** Low- to-mediumdose inhaled corticosteroids and long-acting inhaled β_2 agonists. **Alternative treatment:** Increase inhaled corticosteroids within medium-dose range. Or Low- to medium-dose inhaled corticosteroids and add either leukotriene modifier or theophylline. **If needed:** Increase inhaled corticosteroids within medium-dose range and long-acting inhaled. OrIncrease inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Mild persistent	> 2/wk but < 1/d	> 2nights/mo	≥ 80	20-30	**Preferred treatment:** Low-dose inhaled corticosteroids. **Alternative treatment:** Cromolyn, nedocromil, leukotriene modifierOrSustained release theophylline to a serum concentration of 5-15 µm/ml.
Mild intermittent	≤ 2 d/wk	≤ 2 nights/mo	≥ 80	< 20	No daily medications neededSevere acerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is advised
All patients	Short-acting bronchodilator: 2-4 puffs as needed for symptoms Intensity of treatment depends on the severity of asthma; up to three treatments at 20 min intervals or single nebulizer treatment as needed. Course of systematic may be needed. The usage of short-acting β_2 agonists more than twice a week may indicates a step up to long term control therapy.				

PEF = peak expiratory flow FEV_1 = forced expiratory volume in first second

Key points on guidelines: Inhaled corticosteroids (ICS) are the preferred first-line controller therapy. Cromolyn, leukotriene receptor antagonists (LTRA) and theophylline are listed as alternative therapies (Navarro *et al.,* 2007:s5).

For children older than five years, the guidelines are similar except for the alternative therapy that changes (Navarro *et al.,* 2007:s5):

- Mild persistent asthma also includes nedocromil and sustained-release theophylline.
- Moderate persistent asthma – here one has to increase ICS with no long-acting inhaled β_2 agonists (LABA) or use low- to medium-dose ICS and leukotriene modifier or theophylline.
- The preferred therapy for moderate persistent asthma is to switch to a low- to medium dose of ICS and LABA (one may increase dose if needed)

The EPR-3 Guidelines were designed to assist with the recognition of asthma control and also to improve the management of the disease in asthma patients (Du Plessis *et al.,* 2013:235). The EPR-3 is a lengthy document, but has provided managed health care professionals with the necessary knowledge about asthma diagnosis. The management and further revisions of the NAEPP guidelines are important in the current context where understanding of asthma is increasing and more pharmacologic therapies are becoming available (Urbano, 2008:47).

2.5.2 The PRACTALL Consensus Report published by the European Academy of Asthma and Allergy in 2008

The European Academy of Allergology and Clinical Immunology (EAACI) and the American Academy of Allergy, Asthma And Immunology (AAAAI) teamed up to form the PRACTALL initiative, which published consensus on managing asthma in childhood (Bacharier *et al.,* 2008:5) The PRACTALL guidelines for the management of asthma is comprehensive: covering natural history, pathophysiology and discussion of the heterogeneity of childhood asthma and asthma phenotypes according to the four age groups: 0–2 years, 3–5 years, 6–12 years and adolescents (Bacharier *et al.,* 2008:5). These guidelines were designed for practices in Europe as well as North America (Potter, 2010:6). Thus, these guidelines were not intended for underdeveloped countries (Potter, 2010:7).

In these guidelines, four patterns of asthma are proposed which include recommended strategies for:

- Pharmacological treatment;
- Allergen avoidance;
- Trigger avoidances, and
- Asthma education.

Figure 2.2 indicates the step-wise pharmacologic treatment for asthma in children older than two years of age. The treatment of asthma in children should be given in a stepwise approach according to the severity and frequency of asthma symptoms (Bacharier, 2008:15). Children starting with treatment guidelines should be closely monitored and change where appropriate (Bacharier *et al.,* 2008:15). The following acronyms were used BDP - beclomethasone, ICS – inhaled corticosteroids and LTRA = leukotriene receptor antagonists to efficiently describe the PRACTALL guidelines for asthma treatment and management.

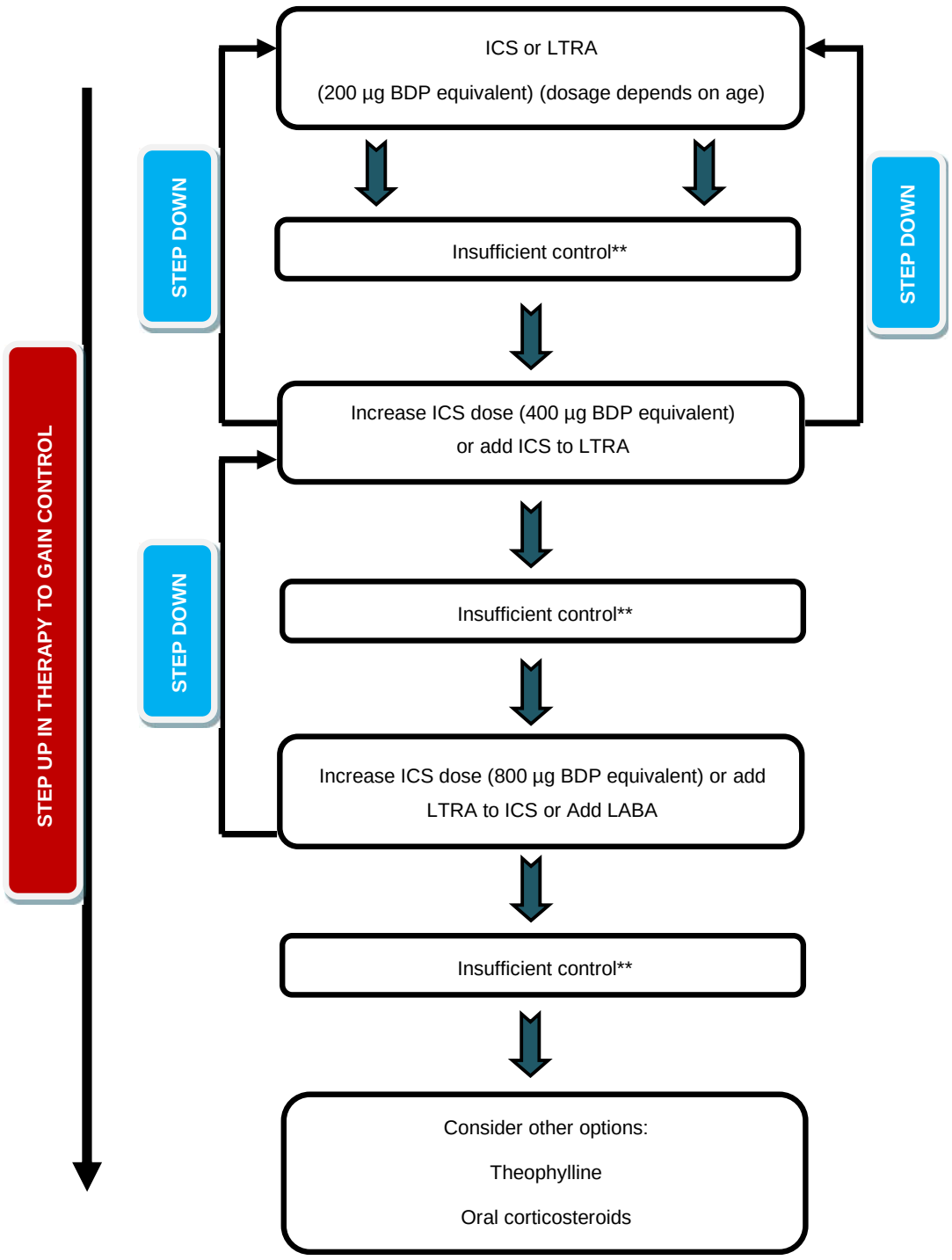


Figure 2.2: **Algorithm of pharmacologic treatment for asthma in children (Bacharier *et al.*, 2008:11)**

The goal of the pharmacologic treatment algorithm is to control and prevent symptoms exacerbations in children with the minimum drug related side-effects (Bacharier *et al.,* 2008:15). The PRACTALL report reviews the natural history and pathophysiology of asthma in children and provides recommendations for diagnosis, practical management and monitoring of the disease (Bacharier *et al.,* 2008:6). The recommendations assist paediatricians and general practitioners working in hospitals or primary healthcare setting to effectively manage asthma in children (Bacharier *et al.,* 2008:6).

2.5.3 The International Primary Care Respiratory Group (IPCRG) Guidelines on the management of chronic respiratory diseases in primary care

The IPCRG was formed in 2001 by primary care specialists with strong links to primary care respiratory groups and global care groups (Tomlins, 2006:71). The IPCRG asked primary experts from several different countries to develop the first primary care guidelines that combined the major chronic respiratory diseases of the developed world (asthma, COPD and rhinitis) in a well-designed format that will provide guidance specially for health care workers (Van der Molen, 2006:35-36). These guidelines focus on the accurate diagnosis of chronic respiratory disease as an essential part of primary care (Bousquet *et al.,* 2006:11). Firstly, asthma should be diagnosed and classified as being either intermittent, mild persistent, moderate persistent or severe persistent, and treated accordingly (Van der Molen, 2006:44). The following pharmacological treatment for asthma was adapted from Van der Molen (2006:38-39):

Step 1: Intermittent asthma: symptoms ≤ once per week – Prescribe patients with a rapid- acting β_2-agonist. Patients over 60 years of age should be given alternative medication such as anticholinergics.

Step 2: Mild persistent asthma: symptoms > once per week – Start with the inhalation of corticosteroids in a low dose of 200 **–** 400 mcg of beclomethasone. If there is no improvement after three months, treatment should be extended to Step 3.

Step 3: Moderate persistent asthma – A combination of inhaled glucocorticosteroids and a LABA as regular treatment. The alternatives are combinations of ICS with sustained release theophylline or with leukotriene modifiers.

Step 4: Severe persistent asthma – If step 3 failed, these patients need special attention. Every effort should be taken to avoid triggers and to promote adherence to the treatment regime. If patients still suffer from asthma attacks, a combination of high dose ICS plus

LABAs should be used twice daily. Other add-on treatments, if necessary, are sustained release theophylline and leukotriene modifiers. For short periods, oral corticosteroids (prednisone 30 mg daily for 7-14 days) can be administered for symptom control.

These IPRRG asthma management guidelines are in line with the GINA recommendations. These guidelines have also been structured in such a way that they can be used in different circumstances across the globe and can be used in any healthcare system.

2.5.4 The Global Initiative for Asthma (GINA) guidelines

In 1989 the GINA programme was launched in partnership with the WHO and the NHLBI (Myers, 2008:755). The initial purpose of GINA was to develop international effective asthma diagnosis and management guidelines that would be valid in both developed and developing countries (O'Byrne, 2010:511). The management of asthma that follows evidence-based practice guidelines often produces better patient results. However, the problem with global evidence-based practice guidelines like the GINA guidelines is that the recommended use of resources are often not available to patients in developing countries (Van Weel *et al.,* 2008:998).

The GINA asthma treatment algorithm consists of five steps of treatment, namely:

Step 1: Rapid–acting β_2-agonists as needed (prn).

Step 2: The low dose ICSs as treatment is also the most effective controller therapy in asthma patients. LTRA are another treatment option but are less effective than the low-dose ICSs.

Step 3: This treatment is aimed at asthma patients whose asthma is not well controlled with low doses of ICUs. Their treatment then consists of a combination of ICSs and LABAs.

Step 4: Treatment is recommended for patients whose asthma is not controlled on low doses of ICSs/LABAs combination. The most effective approach in this step is an increase in the ICSs/LABAs dose, which also includes an add-on therapy of a leukotriene agonist.

Step 5: Treatment is recommended for a small percentage of patients who do not respond to even high doses of ICSs/LABAs drug combination. In addition, the ICSs and LABAs

combination patients will also require oral corticosteroids and omalizumab, a recombinant humanised monoclonal antibody against IgE.

The GINA Guidelines address risk factors associated with development of asthma, diagnoses of asthma and management and pharmacological treatment that include education, control, pharmacotherapy and the management of exacerbations. Table 2.6 presents the algorithm of the GINA guidelines.

Table 2.6: GINA algorithm for the management of asthma: For children older than five years, adolescents and adults (O'Byrne, 2010:513)

Level of control	Treatment action
Controlled	Maintain and find lowest step
Partly controlled	Consider stepping up to gain control
Uncontrolled	Step up until controlled
Exacerbations	Treat as exacerbations

Reduce

Treatment steps

Increase

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education Environmental control				
As needed rapid acting β_2 agonist				
Controller options	**Select one**	**Select one**	**Add one or more**	**Add one or both**
	Low-dose inhaled corticosteroids	Low-dose ICs plus long acting β_2-agonists	Medium- or high-dose ICS plus long acting β_2-agonists	Oral glucocorticosteriods (lowest dose)
	Leukotriene modifier	Medium- or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus Leukotriene modifier	Sustained release theophylline	
		Low-dose ICS plus sustained release theophylline		

The new GINA guidelines also provide detailed management plans for acute exacerbations.

To summarise the GINA guidelines: these guidelines remain rigorously evidence-based and up to date with the most recent studies, but the major hurdle is the implementation of these guidelines by physicians who may be unaware of these recommendations (O'Byrne, 2010:515).

Since the initial development of asthma guidelines in the late 1980's and early 1990's, dozens of different versions of asthma management guidelines have been developed and produced (Myers, 2008:757). Today, the focus of asthma management has shifted from the longstanding acute treatment of a patient to that of long-term control and the prevention of risk factors in the future (Bateman *et al.,* 2010:606). As with all guidelines, algorithms represent an oversimplification of the complex diagnostic issues at hand (Halbert & Isonaka, 2006:17).

Each of the above guidelines provides a unique perspective and important insight into the many problems that clinicians have to deal with when treating patients with asthma; one can see that there are some recommendations in each guideline that are repeated

Although asthma guidelines may not be perfect, they so seem to be the best instrument healthcare workers have to assist asthma patients in receiving the best possible care for asthma (Bousquet *et al.,* 2009:111).

2.5.5 Other national guidelines

Asthma is one of the most common chronic conditions in the world today (Myers, 2008:752). It is therefore essential that clinical practice guidelines must be systematically developed to help practitioners and patients to make appropriate health care decisions in specific circumstances (Jackson & Feder, 1998:427). The four main categories of these early guidelines were: epidemiology, pathophysiology and diagnosis of asthma, pharmaceutical therapies for acute and chronic asthma management, non-pharmaceutical interventions, and asthma education and self-management practices (Myers, 2008:753).

During the 1980's, Australia and New Zealand had more asthma deaths than any other country (Myers, 2008:753). The Thoracic Society of Australia and New Zealand developed a four page-long guideline with a six-step asthma management plan in 1989 (Woolcock *et al.,* 1989:652). These guidelines were, however, inadequate and there was a mounting concern about the problems of these guidelines in these two countries. From here, they proceeded to establish the National Asthma Campaign (Pierce & Irving, 1991:4). Over the past two decades, practice guidelines have been published in Canada, and this publication has led to

the production of evidence-based recommendations regarding optimal care in the asthma patient that are now also used globally (Boulet *et al.,* 2007:329). The evidence-based approach states that guideline strategies should be supported by evidence from rigorous, reproducible, peer-reviewed research (Kallstrom, 2004:784). The finest evidence is obtained by means of a large randomised controlled trail, while the least trustworthy evidence is expert opinion (Kallstrom, 2004:784). The guidelines of the British Thoracic Society recommendations are based on available literature and where evidence is missing, an expert opinion is used. These guidelines have been the most preferred source of information for treating children with asthma (Bacharier *et al.,* 2008:4).

Since those initial guidelines have been promulgated, an assortment of other asthma guidelines has been produced for specific countries in the shape of a global initiative, specific patient populations and for specific clinicians.

2.5.6 South African Guidelines

South Africa has a well-developed health care system, an essential drugs list (EDL) that includes the main drugs that are needed for the management of acute and chronic asthma in both children and adults; an active national asthma education programme, and well-funded societies that are closely involved in the development of evidence based guidelines for the management of adult and childhood asthma (Zar *&* Lalloo, 2013:159). The current updated version of the South African Thoracic Society guidelines was promoted by the need for:

- Incorporation of advances in the pharmaceutical treatment of acute severe asthma,
- Early recognition and objective assessment of acute severe asthma,
- Optimal management and rapid transition to chronic care,
- Prevention of acute attacks, and
- Harmonisation with international guidelines (e.g. GINA).

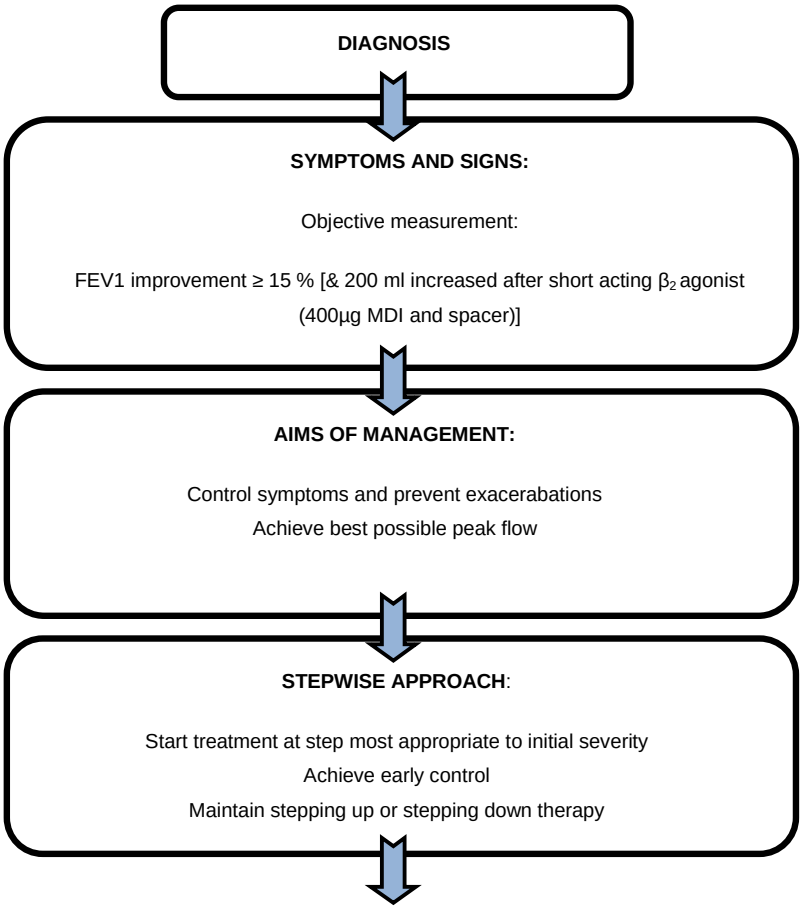
The International Classification of Disease (ICD 10) coding is used by healthcare providers, physicians, hospitals and governments to assess the populations' health and as a means of reimbursement for medical care based on diagnoses and the severity of a disease (Marcus & Braman, 2009:188). The South African Medical Schemes ICD-10 coding for asthma can be seen in table 2.7

Table 2.7: The South African Medical Schemes ICD 10 coding for asthma

- J45 Asthma
- J45.0 Predominantly allergic asthma
- J45.1 Non-allergic asthma
- J45.8 Mixed asthma
- J45.9 Asthma, unspecified
- J46 Status asthmaticus

In this study, the indication for medicine usage was identified by using the ICD-10 code classification system, because it has an international code of diseases and it is thus very relevant to use this classification system.

Two widely used algorithm guidelines (as can be seen in figures 2.3 and 2.4) by the medical schemes of South Africa and the South African Thoracic society are now discussed and compared.



Classification of severity				
Management of chronic asthma in adults				
Classify severity at presentation				
	Intermittent	**Persistent**		
		Mild	**Moderate**	**Severe**
Category	**I**	**II**	**III**	**IV**
Daytime symptoms	≤ 2/week	2-4/week	>4/week	Continuous
Night-time symptoms	≤ 2/week	2-4/month	>4/week	Frequent
PEF (predicted)	≥ 80%	≥ 80%	60-80%	< 60%
Start treatment at most appropriate step				

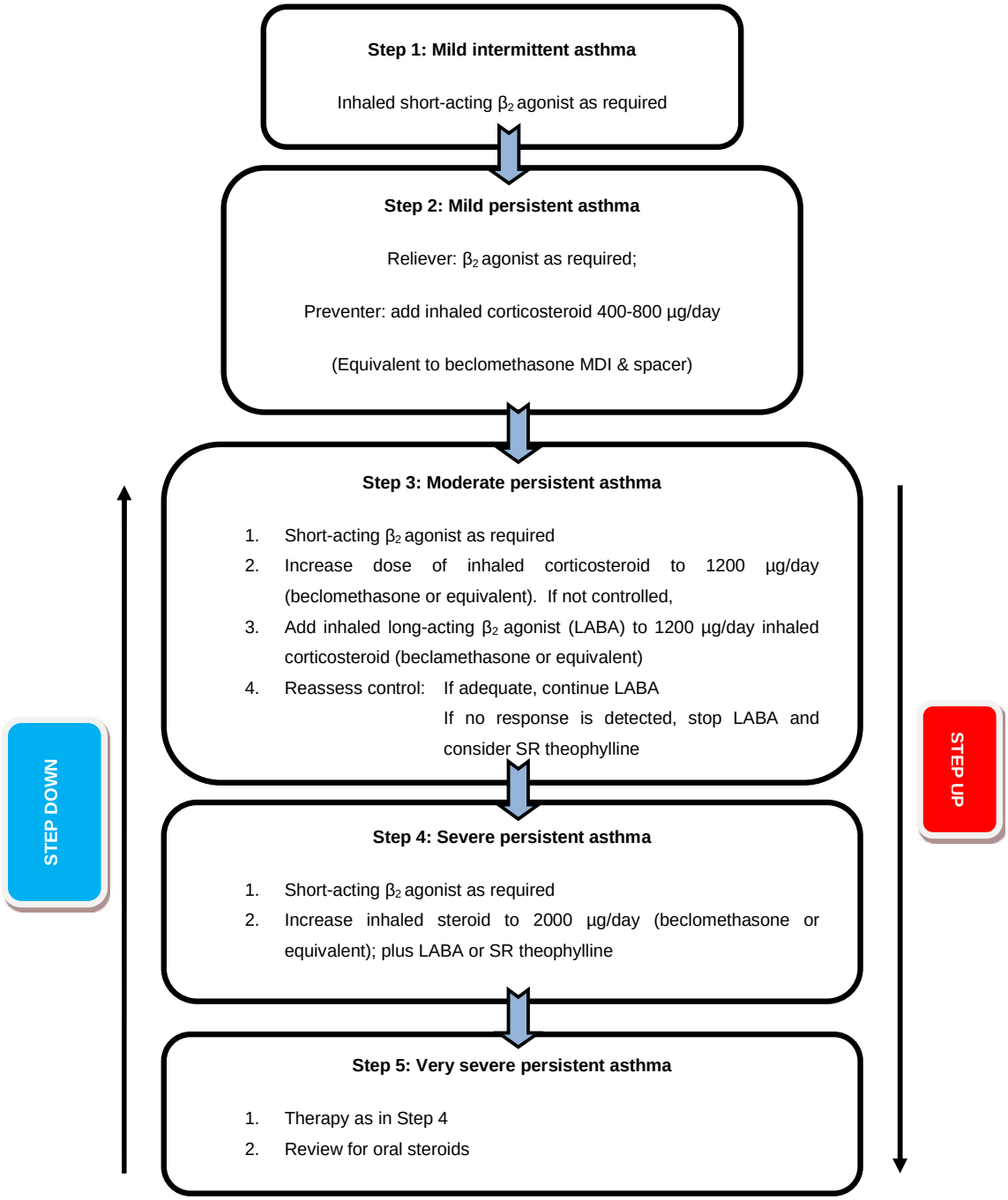


Figure 2.3: **Algorithm for asthma treatment and management by the Council for Medical Schemes of South Africa (CMS, 2013a)**

These guidelines have been designed to ensure the optimal practice care for children and adults with acute asthma, as well as the recommended implementations of long term controller medication for chronic asthma (Zar *&* Lalloo, 2013:159). The guidelines that appear in this chapter are consistent with the international guidelines for the treatment of acute

asthma and have been simplified for ease of implementation in all health care sectors in South Africa. In the updated guidelines acute asthma, also known as asthma exacerbations or asthma attacks as well as other asthma terminology are well defined (Lalloo *et al.,* 2013:191; Kling *et al.,* 2013:201) (refer to section 2.2.5).

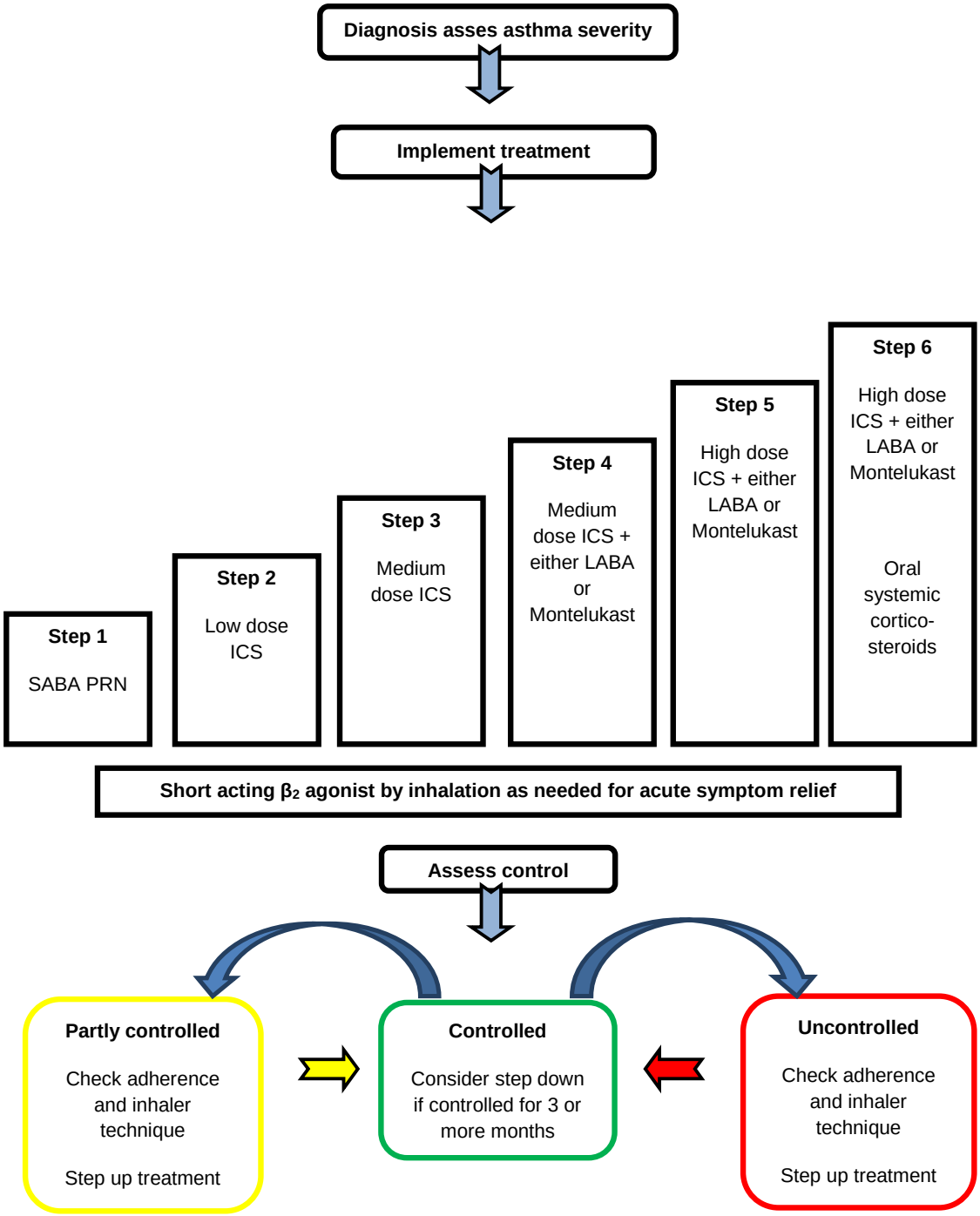


Figure 2.4: Algorithm for diagnoses and management of chronic asthma

The development of country-specific guidelines or local guidelines can provide a more fitting solution for asthma care in individuals and could also account for regional risk factors that influence a patient's choice and adherence to treatment (Price & Thomas, 2006:7). As one can see from the two guidelines set out above, South Africa has the tools to effectively control asthma as a disease, but the challenge we face is to achieve widespread implementation of guidelines (Green *et al.,* 2007:174). It is highly unlikely that there will be any improvement in the current high morbidity and mortality rates with asthma in South Africa if the problem of implementation is not addressed (Kathawaroo & Hukins, 2004:833).

2.6 TREATMENT OF ASTHMA

Asthma medication has been recognised in the literature of ancient civilizations going back almost 2000 years (Weinberger, 2004:6). As regards the situation today, there is currently no cure for asthma. However, with the proper diagnosis, medication and an asthma management plan, the symptoms can be controlled (AAAAI, 2010). The maintenance treatment for asthma patients is determined by the severity on presentation, current asthma medication, patient profile and level of control (Lalloo *et al.,* 2007a:21). These asthma medications are classified according to their use and are comprised of two groups, namely those who are used for long-term control (controllers/anti-asthmatics) and those used for acute relief (relievers**/**bronchodilators) (Papadopoulos *et al.,* 2012:986; Snyman, 2009:14). For the purpose of this study, asthma medications were classified into two main groups using the Monthly Index of Medical Specialities (MIMS®) (Snyman, 2009:152), namely:

Controllers/anti-asthmatics: These medications are taken daily on a long-term basis to keep asthma under clinical control through their anti-inflammatory action. Controlling medication include oral and ICSs, LABAs, leukotriene modifiers, methylxanthines and omalizumab (Cho, 2010:178).

Relievers/bronchodilators: These medications are used on an as-needed basis to relieve asthma symptoms by quickly reversing acute bronchoconstriction. The following are regarded as relievers: short-acting β_2-agonists (SABAs), systemic glucocorticosteroids and short-acting anticholinergics (Cho, 2010:178). Table 2.8 presents a summary of the classification of anti-asthmatics of South Africa by their active ingredient used in the treatment of asthma patients (Lalloo *et al.,* 2007b:32).

Table 2.8: Classifications of drugs by their active ingredient used in the maintenance treatment of asthma adapted from Lalloo *et al.,* (2007:32)

Controllers		Relievers
Anti-inflammatory action to prevent asthma attacks	**Sustained bronchodilator action but weak unproven ant-inflammatory effect**	**For quick relief of symptoms and use in acute attacks as PRN dosage only**
Inhaled corticosteroids 1. Beclomethasone 2. Budesonide 3. Fluticasone 4. Ciclesonide	**Long–acting β_2 agonists** 1. Salmeterol 2. Formoterol	**Short–acting β_2 agonists** 1. Salbutamol 2. Fenoterol 3. Terbutaline
Leukotriene modifiers 1. Montelukast 2. Zafirlukast **Oral corticosteroids** 1. Prednisone 2. Prednisolone 3. Methylprednisone 4. Methylprednisolone	**Sustained–release theophylline preparations**	**Anti–cholinergic** 1. Ipratropium bromide

Currently in the public health care sector of South Africa the EDL is used for the treatment of diseases. The EDL includes national guidelines as well as specific medications that are used for specific diseases (Bateman *et al.,* 2009:71). The aim of asthma treatment is to reduce the patient's symptoms by reducing inflammation, and therefore the choice of medication is based on their anti–inflammatory and bronchodilator effects (Gaga *et al.,* 2007:1049).

Most asthma patients achieve good disease control with the use of ICSs and LABAs – that are the pillar of asthma therapy (Polosa & Benfatto, 2009:114; Agbetile & Green, 2011:1). Asthma treatment for adults and children can be administrated in many different ways, namely inhalation, orally or parenterally. The advantage of inhaled therapy is that the drugs are delivered directly into the airways producing a high concentration with a significant lower risk of systemic side effects (Bateman *et al.,* 2008:149).

The following medications are classified as asthma treatments:

2.6.1 Corticosteroids

Asthma is an inflammatory disease, and corticosteroids are widely recognised to be the most effective and potent anti-inflammatory drugs for asthma (Papiris *et al.,* 2009:2375).

2.6.1.1 Inhaled corticosteroids

Inhalation therapy of corticosteroids was introduced in the late 1970's and allowed the administration of medication with a potent topical effect and small enough dose to treat asthma (Weinberger, 2004:8). It was also proven that ICSs provide a significant better asthma control than the β_2–agonists medication in patients (Kallstrom, 2004:785).

Potential adverse effects: The following effects are associated with corticosteroids: coughing dysphonia, oral thrush (candidiasis), osteoporosis, growth suppression and skin thinning with easy bruising (Motala *et al.,* 2011:13).

2.6.1.2 Oral corticosteroids

Since the effect of corticosteroid medications are not usually seen before six to twelve hours, early administration is necessary (Papiris *et al.,* 2002:38). The treatment regime for oral corticosteroids is usually reserved for patients with severe asthma which cannot be controlled by ICSs in combination with LABAs and other medications (Gaga *et al.,* 2007:1050). These may also be given on a daily basis for severe asthma patients or as a burst treatment for exacerbations (Gaga *et al.,* 2007:1050).

Potential adverse effects: short-term use – The following effects are associated with short-term use of oral corticosteroids: abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension and peptic ulcers (Van Weel *et al.,* 2008:1002).

Potential adverse effects: Long term use – The following effects are associated with the long-term use of oral corticosteroids: growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness and rare impaired immune function (Van Weel *et al.,* 2008:1002).

2.6.2 Long–acting β_2–agonists:

Available for the past decade and a half, these medications were specifically designed for regular use as their duration is at least 12 hours (Walters *et al.,* 2005:385). The β_2–agonists inhaler is so popular that it is discharged around 19 times per second across the globe (Weiss *et al.,* 2006:314). LABAs are used against nocturnal symptoms and exercised-induced asthma (Lalloo *et al.,* 2007a:22). However, LABAs are not safe to use in young children (Green *et al.,* 2007:173).

Potential adverse effects: The following effects are associated with LABAs: tachycardia, skeletal muscle tremor, hypokalaemia and prolongation of QTc interval in overdose (Van Weel *et al.,* 2008:1002).

2.6.3 Leukotriene modifiers

These are the only prescribed asthma medications that are commonly administered orally and are subject to first pass effect in the liver (Tse *et al.,* 2011:390). Patients with aspirin-induced asthma also show a good reaction if treated with leukotriene modifiers (Volkman & Pontikes, 2002:1460). These drugs are, furthermore, safe to use in children of the ages of ≤ 5 years and as an add-on therapy for patient with severe asthma (Bateman *et al.,* 2008:153).

Potential adverse effects: As is the case with a new drug, there are no known specific adverse effects (Van Weel *et al.,* 2008:1002).

2.6.4 Theophylline

Although this medication has been used to treat asthma for over 70 years, its complicated mechanism is still not fully understood (Skoner, 2002:386). Theophylline, in the context of asthma, acts to relax bronchial smooth muscles directly and has some anti-inflammatory properties (Anderson & Thomas, 2010:148; Gaga *et al.,* 2007:1054). Compared to other asthma medications, theophylline has a narrow therapeutic index with a higher incidence of side effects (Anderson & Thomas, 2010:148). Because of this, its role as controller medication is very limited and it is only recommended as a second-line treatment where other options or treatments are unavailable (Weinberger & Hendeles, 1996:1386).

Potential adverse effects: The following effects are associated with theophylline: tachycardia, headache, nausea and seizures (Weiss *et al.,* 2006:316; Van Weel *et al.,* 2008:1003).

2.6.5 Short–acting β_2 agonists:

SABAs constitute a fundamental part in the treatment of asthma (Hashimoto & Bel, 2012:695). The most commonly used SABAs in South Africa are salbutamol and fenoterol (Kling, 2007:37). They relax the smooth muscles around the bronchi via the stimulation of the β_2–receptors and when used as an inhalation, this action occurs within 3-5 minutes (Gaga *et al.,* 2007:1052; Papiris *et al.,* 2009:2372). Because this action is so rapid, SABAs are prescribed for immediate relief of symptoms whenever the need arises (Gaga *et al.,* 2007:1052). SABAs are also the treatment choice to relieve acute asthma symptoms in children because of their wide safe dosage range (Bacharier *et al.,* 2008:15).

Potential adverse effects: The following effects are associated with SABAs: tachycardia, skeletal muscle tremor, hypokalaemia, headache and hyperglycaemia (Van Weel *et al.,* 2008:1003).

2.6.6 Anticholinergics:

While anticholinergic drugs are useful in laboratory setting, their ability to block bronchoconstriction in patients with asthma has been mired by problems surrounding successful dosing, side effects and muscarinic receptor selectivity (Moulton & Fryer, 2011:49). These drugs are used as an alternative bronchodilator for patients who experience side effects from β_2–agonists or who use a large amount of β_2–agonists (Hashimoto & Bel, 2012:695; Peters *et al.,* 2010:1722). Inhaled anticholinergics must not be used for the long-term management of asthma in children (McDonald & Bara, 2003:1).

Potential adverse effects: The following effects are associated with anticholinergics: drying of mouth and respiratory secretion with increased wheezing in some patients (Van Weel *et al.,* 2008:1003).

To effectively treat asthma, a patient requires a combination of pharmacology and psychology (Horne, 2006:69). The implementation of guidelines-based therapy seems to be effective in the prevention and treatment of child and adult asthma patients throughout the world (Nagai, 2012:71).

2.7 CO-MORBIDITY

Asthma is frequently associated with various co-morbidities including rhinitis, sinusitis, gastro-oesophageal reflux disease, obstructive sleep apnoea, hormonal disorders and psychopathologies (Boulet & Boulay, 2011:377). In a recent study by Sullivan *et al.* (2011:367) it was found that an individual with asthma had a greater co-morbidity, reporting twice as many co-morbid conditions as those who do not suffer from asthma. These findings have also been correlated with poor asthma control, decreased quality of life and increased health care use for asthma patients (Gershon *et al.,* 2012:11). The core management of asthma is now too recognized and identify co-morbidities, particularly in more severe forms of the disease (Boulet, 2009:902; Gershon *et al.*, 2012:11).

The most common co-morbidities associated with asthma are discussed below.

2.7.1 Anxiety disorder

Anxiety disorder includes six symptoms associated with general anxiety disorders, which include: restlessness, fatigue, difficulty concentrating, irritability, muscle tension and sleep disturbance (Comer *et al.,* 2012:995). Both anxiety disorders and asthma have a high prevalence in children, adolescents and adults. This suggests that that these disorders frequently co-occur (Katon *et al.,* 2004:355). Health care professionals should also be aware that patients with asthma become more anxious; especially patients who suffered near-fatal asthma attacks are particularly vulnerable (Bosley *et al.,* 1996:456).

2.7.2 Depression

Depression is a common mental health disorder and is characterised by low self-worth, disrupted sleep or appetite, sadness, loss of interest or pleasure, feelings of guilt, tiredness and poor concentration (WHO, 2012). Adults with asthma have an increased risk to develop mental disorders. These mental comorbidities are associated with an increase in health

problems for the patients and could lead to the worsening of existing medical conditions (Gomutka & Szczepaniak, 2012:320). Depressive symptoms are common in older asthmatic individuals. This in turn increases the health-related risk factors of a patient that may impact on the severity and direction of asthma (Goral et al., 2012:22). Investigations into the prevalence of depression in asthmatic patients have reported findings ranging from 1% to 45% of a population. This indicates that asthma patients also tend to suffer from depression or depressive symptoms (Opolski & Wilson, 2005:3). The cumulative prevalence of depressive symptoms was twice as high in adolescents with asthma as those without asthma (Opolski & Wilson, 2005:3). These findings suggest that asthma is a risk factor for depression in adolescents. This is not surprising, as asthma affects daily functions that would require physical activity such as movement and school activities as well as psychosocial functioning (Lu *et al.,* 2012:707). Family doctors, paediatricians and healthcare providers should develop strategies in to detecting depressive symptoms in adolescents with asthma and offer psychological interventions to reduce the burden of psychiatric co-morbidity (Lu *et al.,* 2012:713).

2.7.3 Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a disorder entailing that a patient frequently stops breathing during their sleep as a result from upper airway obstruction (Park *et al.,* 2011:549). OSA is a common problem associated with asthma, as proved by Yigla and co-workers (2003:866). These authors conducted a prospective cohort study in 20 patients with severe unstable asthma and found a high prevalence of OSA among those who received long-term chronic oral corticosteroid therapy (Yigla *et al.,* 2003:866). It has also been shown that OSA may contribute towards poor asthma control in patients (Dixon *et al.,* 2011:703).

2.7.4 Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) affects individuals with a reflux of gastric contents into the oesophagus, causing symptoms like heartburn, dysphagia, nausea and epigastric pain. It also causes a less prevalent extra-oesophageal manifestation that includes coughing, a sore throat, wheezing and shortness of breath (Armstrong *et al.,* 2005:18). Asthma patients are three times more likely to be affected by GORD compared to the general population (Bateman *et al.,* 2008:165). GORD could, in fact, worsen asthma severity either by direct effect on airway responsiveness or via aspiration-induced inflammation (McCallister

et al., 2010:144). Furthermore, asthma medication like theophylline and β-agonist may cause GORD symptoms (McCallister *et al.,* 2010:144). This suggests a cruel cycle between asthma medication and GORD symptoms (Boulet & Boulay, 2011:382).

2.7.5 Migraine

Migraine is a recurrent neurovascular headache disorder and is characterised by episodes of severe throbbing headache associated with vomiting and nausea, photophobia, photopia and immobility (Katsnelson *et al.,* 2009:667; Machado *et al.,* 2010:206). Women with a history of migraine had statistically significant higher odds of suffering from asthma when compared with non-migraine sufferers, but the pathogenesis for co-morbid migraine and asthma patients remains unknown. However, researchers have speculated that migraine and asthma may share some common etiologic factors (e.g. genetic, biochemical or environmental factors) and that an underlying relationship exists between them (Czerwinski *et al.,* 2012:7).

2.7.6 Rhinitis and Chronic Sinusitis

Rhinitis is defined as an inflammation of the lining of the nose and is characterised by nasal symptoms including anterior and posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose (Bousquet, 1998:938). A large percentage of asthmatic patients are affected by allergic rhinitis, which is often undiagnosed and untreated. It is suspected that 20% – 50% of patients with allergic rhinitis also have asthma and that more than 80% of patients with asthma have rhinitis (Boulet & Boulay, 2011:379). Rhinitis may influence asthma through various mechanisms including the release of mediators into the airways or peripheral circulation which causes the inflammation of the lungs and bronchoconstriction of the airways (Boulet, 2009:898). It has previously been shown that the combination of asthma and rhinitis increased the risk of short-term sickness absence from work (Hakola *et al.,* 2011:1598). These two conditions may be linked via common genetic and environmental factors which are well documented (Gershon *et al.,* 2010:616).

As far as sinusitis is concerned, it is a disease with persistent upper respiratory infection symptoms with non-specific complaints such as nasal congestion, nasal discharge, fever and cough (Barbi & Longo, 2007:23). It has been reported that almost 90% of patients with

mild to moderate asthma, and almost 100% of those with severe asthma, have some sort of abnormalities of the sinuses (Bresciani *et al.,* 2001:77).

2.7.7 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gasses (GOLD 2006). COPD has also been called "the hidden epidemic" with the diagnosis of the disease often remaining ubiquitous and unrecognised by health care workers (Enarson, 2004:157). There are approximately 210 million people who suffer from COPD in the world today, and it is the fourth leading cause of death. It is expected that by 2030 it will take the number three spot (WHO, 2008b). In Africa, it may soon surpass deaths caused by HIV/AIDS (WHO, 2008b).

Asthma and COPD in sub-Saharan Africa are under-recognised, under-diagnosed, under-treated, and inefficiently prevented (Van Gemert *et al.,* 2011:240). Asthma and COPD are not always easy to differentiate. Nevertheless, in most cases both diseases have distinctive characteristics that result in different patterns of treatment (Miravitlles *et al.,* 2012:72). It is for this reason that the combination of asthma and COPD is a major cause of mortality and disability for all age groups globally (Bousquet *et al.,* 2003:265). In many of these patients with chronic respiratory diseases, it is very difficult to distinguish between asthma and COPD (Bousquet *et al.,* 2003:275). There is a great need to provide local health care workers with the necessary information to differentiate and control asthma and COPD (Van Gemert *et al.,* 2011:245).

In a recent study by Gershon and co-workers (2013:617), the evidence indicates that asthma co-morbidity appears to be a common occurrence and has a significant effect on individuals with asthma, but also the healthcare system as a whole (Gershon *et al.,* 2013:617).

Despite the importance of co-morbidities in asthma this has been a relatively under-recognised and understudied area, as evidenced by the comparative lack of literature on this issue, and its absence from asthma guidelines (Reddel *et al.,* 2009:59). When these co-morbid conditions are recognised early and treated adequately, better asthma control is obtained for the patient (De Groot *et al.,* 2010:675).

2.8 THE BURDEN OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic respiratory diseases like asthma and COPD are associated with enormous healthcare expenditures that include both direct costs, in the form of hospitalisations and medications, and indirect costs in the form of loss of work which is a combination of directly missed days of work/school that occur during exacerbation and the loss of future potential earnings associated with both morbidity and mortality. Asthma is ranked as the eight leading contributor to the list of disease burden in South Africa according to study done by Bradshaw et al. (2007).

2.8.1 Mortality and morbidity

Accurate information on the causes of death in developing countries is essential with a view to develop national and international health care policies for the prevention and control of diseases like asthma and COPD (Bousquet *et al.,* 2003:267). It is estimated that asthma accounts for 1 in every 250 deaths worldwide, while COPD causes around three million deaths in the world each year (Stanciole *et al.,* 2012:1). These deaths usually occur in patients' homes, after the severity of asthma was underestimated and underrated – which usually means that the patients had been inadequately treated prior to the attack (Aït-Kaled *et al.,* 2001:973). Many of these deaths are preventable with the correct medication (Masoli *et al.,* 2003:2). Together the morbidity, mortality and cost associated with asthma are imposing an ever-increasing burden on society (Kim *et al.,* 2011:34).

2.8.2 The economic burden of asthma

In South Africa there is a clear sign that the magnitude of the burden of asthma is under-appreciated; the reason for this is that the health care system is overburdened by infectious respiratory diseases like pneumonia and tuberculosis (Zar *&* Lalloo, 2013:159). The total cost of caring for asthma has been calculated by the WHO to exceed that of HIV/AIDS and tuberculosis, with expenditure reaching nearly $13 billion annually in the United Sates alone (Lavoie *et al.,* 2006:1040).

A Medical Expenditure Panel Survey (MEPSs) analysed by Barnett and Nurmagambetov (2011:148) between 2002 and 2007, found that the value of additional days lost per year to asthma contributed to almost $301 per worker and a $91 per student living in the United

States of America (Barnett & Nurmagambetov, 2011:148). A recent study by van Ganse and colleagues (2006:144) in three European countries found that the cost of asthma per patient increased with the increase of co-morbidities and asthma severity, as classified by GINA (Van Ganse *et al.,* 2006:144).

The heavy economic burden attributable to asthma is a result of the high prevalence of the disease, coupled with the significantly increased medical expenditures and productivity loss (Sullivan *et al.,* 2011:363).

2.8.3 The socio-economic burden

A disease like asthma usually constitutes a significant burden on patients' lives, leading to chronic episodic and often dramatic effects (Sullivan *et al.,* 2011:363). Asthma patients are less productive and more likely to be unemployed, spend more days sick in bed and are more likely to have limitations or inabilities in terms of day to day activities than those without asthma (Sullivan *et al.,* 2011:367). It has been suggested that children/adolescents with asthma are even more likely to be bullied because their peers view them as vulnerable (Blackman & Gurka, 2007:93).

All of these factors are likely to contribute towards the socio-economic morbidity and mortality associated with asthma and COPD in South Africa as set out above, as well as widening the gap between the private and public sector in health care.

2.9 CHAPTER SUMMARY

In this chapter, asthma as a disease was scrutinised. It is a chronic inflammation of the airways that has affected people throughout known human history. With the modern development of a definition for asthma, a better understanding of the disease itself was achieved. In spite of this new information, the prevalence of asthma is increasing worldwide as well as in South Africa, where the mortality and morbidity rates are among the highest. Asthma is currently considered to be the most prevalent chronic disease among children. The greatest risk factor associated with asthma is smoking, but most asthma patients are susceptible to a great variety of stimuli that include pollen, viruses and hormonal disturbances.

Asthma management has come a long way since the 1980's. There are organisations like GINA and NAEPP that monitor asthma as a disease while developing classification systems and treatment guidelines, internationally and nationally. Currently, the public health care sector in South Africa has the EDL that specifies asthmas' medications that are available for use, together with national guidelines.

Asthma medication can be classified into two groups, namely controllers and relievers – of which the combination of corticosteroids and LABAs is the most effective in treating asthma.

A number of co-morbidities are associated with asthma. These can include the following: anxiety disorders, depression, OSA, GORD, migraine, rhinitis, chronic sinusitis and COPD. Asthma, together with one of these co-morbidities, can greatly affect a patient's health and contribute not only to the social and economic burdens of a country, but also to the morbidity and mortality rates if not correctly diagnosed, treated and resolved.

Asthma and COPD are common conditions that dominate the occurrence of obstructive airway diseases among the general population. The cost involved in treating asthma and also COPD has an impact on the lives of patients; indeed, the global economic burden of asthma is increasing rapidly.

In the next chapter the methodology and drug utilisation as well as its application in this study are discussed.

CHAPTER 3

EMPERIAL STUDY

3.1 INTRODUCTION

Asthma is an auto-immune disease of the airways that, with the right medications and treatment regime, can be well controlled but not cured. Using the wrong medications or inefficient treatment regime can have a significant and detrimental effect on a patient's quality of life. Therefore, it is vitally important to understand exactly what asthma is as a disease, and to take full cognizance of the treatment options and regimes available for effective treatment.

As mentioned in the problem statement set out in Chapter 1, the study focuses on identifying the prescribing patterns of asthma therapy and treatment in a portion of the private healthcare sector a South African pharmaceutical benefit management (PBM). These prescribing patterns will be identified and classified according to the medicine claim database.

This methodology chapter is part of the scientific processes aimed at identifying the most adequate set of methods for guiding researchers and analysing data. The research methodology, the procedures followed for acquiring the necessary information and the statistical analyses of the data are discussed here.

3.2 RESEARCH OBJECTIVES

The research project includes two primary research objectives, namely; general research objectives and specific research objectives. These are addressed below:

3.2.1 General research objectives

The general and overall research objective of this study is to determine the prescribing patterns and cost of asthma therapy and treatment in a portion of the private health sector of South Africa. This main objective of this current study will be achieved by using the medicine claims database of South Africa.

3.2.2 Specific research objectives

The specific research objectives that have been formulated based on an overview of the literature are:

- To review asthma severity as an illness with prevalence, risk factors and the treatment guidelines thereof, and
- To review asthma co-morbidities, especially with COPD and the cost implication thereof.

The first specific research objective has already been accomplished in the literature overview in Chapter 2. In this chapter, the focus is on addressing the empirical research objectives, which are:

- To determine the prevalence of asthma from the year 2008 to 2011 stratified by age group, gender and geographical distribution,
- To investigate the influence of gender and age on the prescribing patterns of asthma prescriptions and items according to the database and the cost-implication thereof, and
- To determine the medicine costs of treating asthma from the year 2008 to 2011 and the influence of age groups, gender and the cost incurred by the third-party payer as well as the patient (in form of levies),
- To determine the generic influence on asthma medication and the cost implication thereof and
- To investigate the prevalence of COPD in asthma patients and the cost-implication thereof.

3.3 EMPIRICAL STUDY

Empirical research entails applying observation and experience as the main modes for gathering information. Empirical evidence can be divided in to qualitative and quantitative analyses which, in turn, are used to answer empirical questions (questions mentioned in Chapter 1). This process can be observed as accurate and involves a great deal of planning from the researcher. For this study, empirical research involves obtaining and analysing data,

collected from the PBM, to arrive at the results of the study. Certain conclusions are then drawn and recommendations are made.

3.3.1 Research design

A quantitative retrospective drug utilisation study was conducted on medicine claims data of a South African PBM company to determine the prescribing patterns and cost of asthma therapy in a segment of the South African private health care population for the period 1 January 2008 to 31 December 2011.

A drug utilisation review is a technique used by prescription drug programme administrators and PBMs to manage drug utilisation (Fulda *et al.,* 2004:434). The definition of a drug utilisation review (DUR) by Brodie and Smith (1976:143) is that it is *"an authorised, structured, and continuing program[me] that reviews, analyses and interprets patterns of drug usage in a given health care system"*. Thus, the main purpose of a DUR programme is to reduce or eliminate serious and preventable drug-related morbidity (Fulda *et al*., 2004:433).

The two DUR methods that are widely recognised are prospective DUR and retrospective DUR review (Fulda *et al.,* 2004:433). Prospective DUR involves reviewing each prescription for an individual patient before it is dispensed with a view to identify drug-related problems such as drug-drug interactions or drug-disease contraindications, therapeutic duplication or other potential adverse drug effects (Lyles *et al.,* 2001:76).

Retrospective DUR, on the other hand, can be used to identify problems occurring in prescribing patterns through analysis in order to identify the use of high-cost drugs, to compare particular classes of drug use by different facilities or providers, or to monitor adherence to pharmacotherapy recommendations from treatment guidelines for the specific disease (Lyles *et al.,* 2001:76). These occur after the patient has completed a course of therapy or while the patient is receiving chronic medication and aims to prevent future costly behaviour on the part of the prescriber (Guo *et al.,* 1995:1175; Soumerai & Lipton, 1995:1641). One limitation of DUR systems is the emphasis on evaluating overall drug cost without regard to the effect on the individual patient (Anis *et al.,* 1996:637).

This stage of the study consists of six phases, namely:

- Selection of the research design.
- Selection of a study population.

- Selection of the measuring instruments.
- Data analysis.
- The report and discussion of the results of the empirical investigation.
- Recommendations based on the results of the empirical investigation.

3.4 DATA SOURCE

The data was extracted from medicine claims data of a PBM company in a section of the private health care sector of South Africa. A PBM company is a set of defined benefits that ensures all medical scheme members have access to certain minimum health services. The PBM oversees a large and very important industry consisting of about 97 medical schemes in South Africa with around 8 49 784 beneficiaries. The data obtained represented a period of four years stretching from 1 January 2008 to 31 December 2011. The data was analysed in periods of 12 months at a time. The overall time period was therefore divided in to four annual periods ranging from January to December 2008, January to December 2009, January to December 2010 and January to December 2011.

The following fields were used in the study:

- Date of treatment.
- ICD-10 coding of asthma.
- Date of birth of the patient (to determine age groups).
- Gender.
- Postal codes of prescribers.
- Indicator for generic products.
- Active ingredients of medications.
- Cost of prescriptions and medicine items which include the cost incurred by the third-party payer as well as the patient (in the form of levies).

3.5 THE TOTAL AND ASTHMA POPULATION OF THIS STUDY

The total population (i.e., the total database) consisted of the medicine claims collected from the database for the period 1 January 2008 to 31 December 2011. From the total database, all the asthma prescriptions were extracted (asthma database or study population).

The inclusion criteria for the asthma study population were composed in the following manner:

- Patients who suffered from asthma as classified by the Chronic Disease List (Refer to Appendix B).
- Patients who had used medication for asthma as classified by the ICD-10 coding J45 for asthma and J46 for status asthmaticus (Marcus & Braman, 2009:188) (refer to Appendix B).
- Asthma patients who had used medication for COPD as classified by the ICD-10 coding J44 for unspecified COPD and J43 with acute exacerbations (Marcus & Braman, 2009:188) (refer to Appendix B).

The asthma study population was extracted from the total population. The total population comprised of a total of 4 580 148 patients and asthma (45 832) made up 1.00% of patient on the database from 2008 to 2011.

3.6 DATA ANALYSIS

The ideal way to analyse data, as stated by Donath and colleagues (2013:14), is to have a clearly developed study protocol before the analysis commences. This ensures that information is collected in a way that can answer the research questions and thus avoids collecting unnecessary information (Donath *et al.,* 2013:14). Using a clear analysis plan that has been developed before the data has been examined renders the study findings more credible and helps the researcher to avoid having to make important decisions after the event (Donath *et al.,* 2013:14).

3.6.1 Data analysis organogram

The data was analysed by means of certain steps, as explained in figure 3.1. The Statistical Analysis System SAS 9.3® was used to extract and analyse data from the database. Microsoft Word 2010® and Microsoft Excel 2010® were used to create basic tables and figures and to compute certain statistical measures. The data will be discussed in greater detail in Chapter 4.

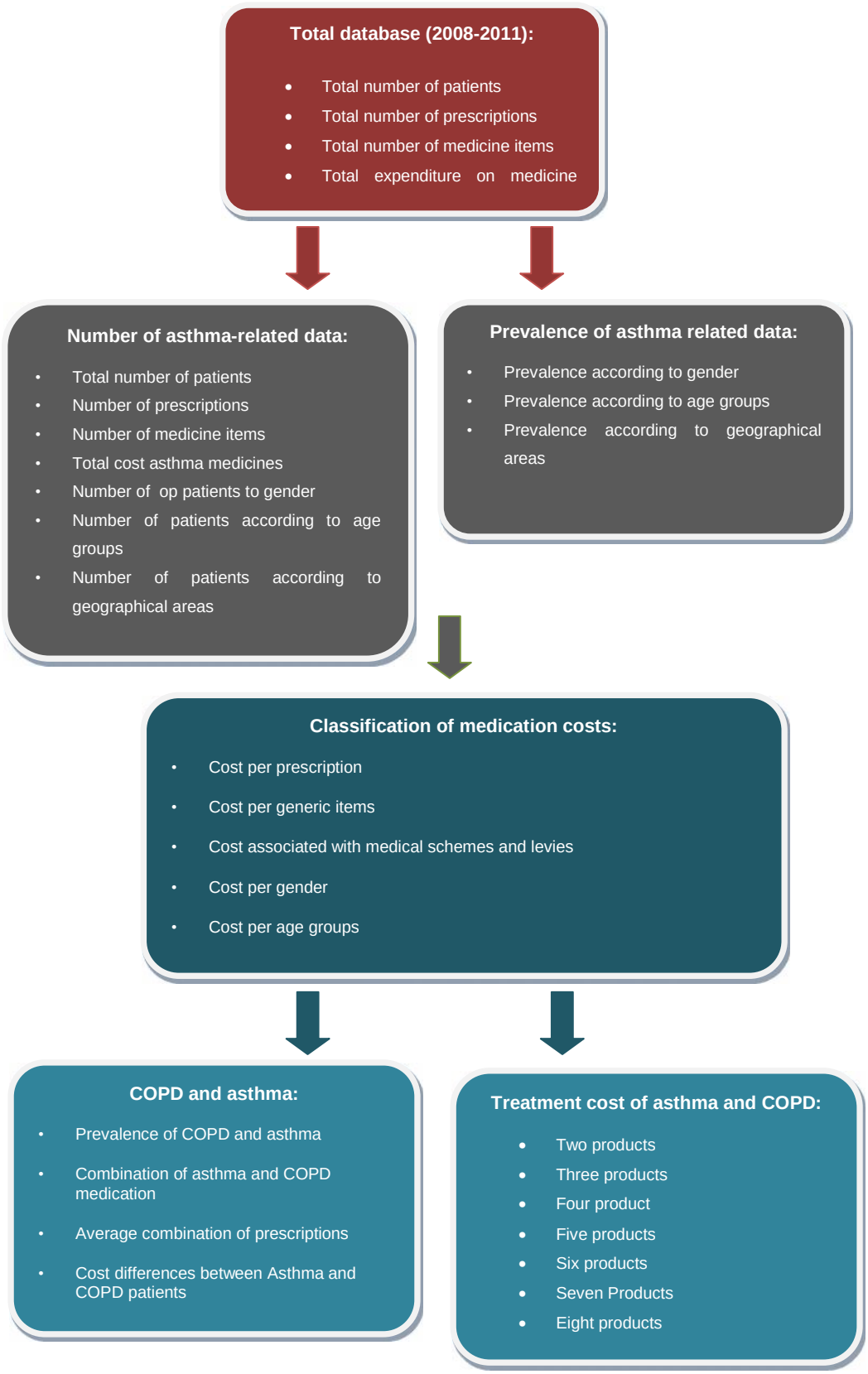


Figure 3.1: Organogram of data presentation

3.6.2 Study variables

For this study, the data was divided into different categories. These are explained below.

3.6.2.1 The MIMS® classifications system

The MIMS® classification system is based on dividing pharmaceutical products in to groups according to their pharmacological action by their active ingredients (Snyman, 2009:152).

3.6.2.2 Type of medication

The type of medication that is used by patients whose data was used in the study was classified by using the MIMS® classification system. This classification system is based on dividing pharmaceutical products into their pharmacological action (Snyman, 2009:152). For the purpose of this study, the medication was divided into 10.2 (bronchodilators) and 10.4 (anti-asthmatics) as stated by the MIMS®.

3.6.2.3 Age groups

Age is calculated by means of a patient's date of birth. In this study, it was possible to calculate the age of a patient using the date of birth as indicated on the prescription that was claimed through the medicine claims database. The age of patients was calculated from 1 January of the year following the date that the prescription was dispensed. For example, if the prescription was dispensed to a patient in August 2007, the age of the child would be taken as age of the child as on 1 January 2008.

Patients that fall under the following age groups were used to determine the asthma population:

- Age group 1 (AG1): 0 – 7 years
- Age group 2 (AG2): > 7 ≤ 18 years
- Age group 3 (AG3): >18 ≤ 45 years
- Age group 4 (AG4): > 45 ≤ 65 years
- Age group 5 (AG5): > 65 years

The age of a patient is usually considered when determining the drug dosage for paediatric use; furthermore, dosages are generally based on the following age groups: 2 to 6 years old, 6 to 12 years old, and over 12 years of age (Ansel, 2012:124).

3.6.2.4 Gender

Gender may refer to certain socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women. In this study, gender will more simply refer to biological sex: men and women. This is done to determine whether the data suggests gender-based differences among the asthma population.

3.6.2.5 Geographical area

There are different trends associated with asthma and urbanisation and geographical location in South Africa. To address this variable, data from the nine provinces will be compared. The prescriber's postal codes were used to differentiate between provinces. Patients were divided into the following geographical areas: Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, Northern Cape, North-West and Western Cape.

These geographical areas were included to study the effect of urbanisation on the prevalence of asthma in the South African population (refer to 2.4.2.2).

3.6.3 Research measurement

The following instruments were used to analyse the data:

3.6.3.1 Prevalence

According to the online Oxford English Dictionary (2013), prevalence can be defined as the total number of cases of a disease in a given population at a specific time. In this study, the prevalence of the number of asthma and COPD patients, prescriptions and medicine items were viewed as parallels, depending on the type of prevalence that was determined.

The following categories are used to determine the prevalence of asthma:

- The prevalence of all prescriptions and medicine items claimed throughout the PBM database of all patients from January 2008 to December 2011.
- The prevalence of all prescriptions and medicine items claimed throughout the PBM database by asthma patients from January 2008 to December 2011.
- The prevalence of all asthma prescriptions and medicine items in asthma patients between the different age groups, genders and geographical areas.
- The prevalence of all asthma prescriptions and medicine items in asthma patients' age groups and gender combined.

3.6.3.2 Cost

Estimating the national expenditure for asthma treatment can provide useful information to guide clinicians and policy makers on improving the management of asthma thorough better treatment (Al-Busaidi *et al.,* 2013:219). The total cost will include all cost incurred by the third-party payer as well as the patient (in the form of levies). In this study, the cost of asthma was expressed as Rand Value (R) and the focus was only on the medication claimed through the PBM. The cost was divided into total cost, cost of levy by the patient and cost due from the medical scheme.

In the following chapter, the cost of asthma medicine will be determined for the following sets:

- The cost of all medicine items claimed through the database from January 2008 to December 2011
- The cost of asthma medication items claimed through the database from January 2008 to December 2011.
- The cost to patients (levies) for asthma medication items claimed through the database from January 2008 to December 2011
- The cost to third-party players (medical schemes) for asthma medication items claimed through the database from January 2008 to December 2011
- The cost of asthma medication items claimed, according to age group, gender and geographical areas through the database from January 2008 to December 2011
- The cost differences of medicine items between asthma and asthma/COPD claimed through the database from January 2008 to December 2011.
- The cost of generic indicators for asthma medication items claimed through the database from January 2008 to December 2011

3.6.3.3 Cost prevalence index

The cost-prevalence index (CPI) shows the relative expensiveness of medicine (Serfontein, 1996:119). The CPI can be interpreted as seen in equation 3.1:

$$\text{CPI} = \frac{\text{Cost } \%}{\text{Prevalence } \%}$$

Equation 3.1: Statistical formula for calculating the CPI (Serfontein, 1996:119)

- If the CPI is < 1, the drug item is relatively inexpensive.
- If the CPI is = 1, there is an equilibrium between cost and prevalence of the drug item.
- If the CPI is > 1, the drug item is relatively expensive.

In this study, the CPI was used to evaluate the stability between cost and prevalence in asthma medicine items to determine which could be described as relatively expensive and inexpensive. The CPI was also used to describe if asthma or asthma-COPD medicine items were more expensive than the other.

3.7 STATISTICAL ANALYSIS

Statistics can be defined as the science of collecting, organising, analysing and interpreting data in order to make decisions (Asadoorian & Kantarelis, 2005:2). Statistics can be further divided into two main categories, namely descriptive statistics and inferential statistics. Data analysis was conducted by means of the SAS 9.3® computer package and was analysed for a number of 12 month time periods. The data was then analysed by applying the concepts of descriptive and inferential statistics.

3.7.1 Descriptive statistics

Descriptive statistics can be defined as the collection, presentation, analysing and interpretation of a data set (Pérez-Vicente & Expósito Ruiz, 2009:314). The main function of descriptive statistics is to summarise the above-mentioned features of analytical statistics in order to extract a set of values that can be interpreted. Descriptive statistics entails the

discipline of quantitatively describing the main features of a collection of data, or the quantitative description itself (SSC, 2006). Descriptive statistics is distinguished from inferential statistics in such a way that descriptive statistics aims to summarise a sample, rather than apply the data towards learning more about the population that the sample of data is thought to represent. Even when a data analysis draws its main conclusions using inferential statistics, descriptive statistics is generally also presented.

Descriptive statistic is therefore used to summarise or describe any data, in any sample size (Pérez-Vicente & Expósito Ruiz, 2009:314). This statistics summarises the data with the purpose of describing what occurred in the sample (Allua & Thompson, 2009:168).

The following descriptive statistical methods were used to analyse the data:

3.7.1.1 Average value (mean)

The mean (also known as the average) is obtained by dividing the sum of the observed values by the number of observations. It is easily understood and has useful mathematical properties that make it convenient for use in many statistical contexts. The formula for the mean is given below as equation 3.2:

$$\tilde{x} = \frac{\Sigma \sum x}{n}$$

Equation 3.2: Statistical equation for determining the mean (Whitley & Ball, 2002:66)

Where:

$\tilde{x}$ = mean

Σ = The sum

n = The number of observations

x = The values of observations

Continuous variables are summarised using the mean or average of the data (Donath *et al.,* 2013:15).

For the purpose of this study, the mean was calculated for the total number of prescriptions per year and per patient, the number of medicine items per prescription and on the total database, the total cost of these medicine items, the total cost per prescription and the total cost of all medicine. These calculations were also repeated for the asthma database that includes prescriptions, medicine and cost of items and prescriptions.

3.7.1.2 Standard deviation

The standard deviation (the square root of variance) can be used to estimate a population's true variance. The formula of standard deviation (SD) is given in equation 3.3 (Keller 2012:2).

$$s = \sqrt{\frac{\Sigma(x - \tilde{x})^2}{n - 1}}$$

Equation 3.3: Statistical equation for calculating the SD (Keller 2012:2)

Where:

s = Standard deviation

x = Value of the variable

$\tilde{x}$ = Arithmetic mean

n = Number of observations

The SD measures how far away from the mean the observations are on average (Donath *et al.,* 2013:13). It thus summarises a great deal of information in one number and, like the mean, has useful mathematical properties (Whitley & Ball, 2002:3).

For the purpose of this study, the SD was calculated for the total number of prescriptions per year and per patient, the number of medicine items per prescription and on the total database, the total cost of these medicine items, the total cost per prescription and the total cost of all medicine. These calculations were also done for the asthma database that includes prescriptions, medicine and cost of items and prescriptions.

3.7.1.3 Confidence Intervals

Confidence intervals (CI) are a range of values calculated from the sample of observations and are believed to contain, with a particular probability, the true value (Donath *et al.,* 2013:14). The CI is a range of values likely to include the true unknown value (Alam *et al.,* 2005:463). The smaller the sample size is, the wider the CI. As the sample becomes larger, researchers are increasingly certain that the truth is not far from the point estimate that was observed from the data (Guyatt *et al.,* 1995b:170). The boundaries of the CI are based upon the sample mean and its standard error. The 95% CI for a mean is expressed in equation 3.4 (Alam *et al.,* 2005:463):

Mean x units, 95% CI y to z units.

Equation 3.4: Statistical equation for calculating CI (Alam *et al.,* 2005:463).

CI may be reported in 90%, 95% or 99% intervals. In the case of a 99% CI, there will only be 1% risk that the interval will not contain the true value. Although reducing uncertainty is desirable, it should be understood that the 99% CI will be much wider than the corresponding 95% CI, just as the 95% will be wider than the 90% interval (Alam *et al.,* 2005:464).

The 95% CI was used in combination with the following averages: the total number of prescriptions per year and per patient; the number of medicine items per prescription and on the total database; the total cost of these medicine items; the total cost per prescription; and the total cost of all medicine. These calculations were also done for the asthma database that includes prescriptions, medicine and cost of items and prescriptions

3.7.1.4 Percentage

The percentage is a portion (number of observations with a given characteristic divided by the total number of observations) multiplied by 100% as defined by the online Oxford English Dictionary (OED, 2012).

3.7.1.5 Standard error

The standard error can be defined as a statistical term that measures the accuracy with which a sample represents a population (Li & Hung Wong, 2001:2). In statistics, a sample mean deviates from the actual mean of a population; this deviation is called the standard error. The smaller the standard error, the more representative the sample will be of the overall population. Also, when the sample size is large, the smaller the standard error is because the statistics will approach the actual value (Li & Hung Wong, 2001:2).

3.7.2 Inferential statistics

Inferential statistics can be defined as set of techniques used to arrive at conclusions from the population through the manipulation of sample data (Pérez-Vicente & Expósito Ruiz, 2009:314). It is the process of formulating generalisations about the population from a representative sample of data. Inferential statistics is based upon the probability theory as well as on hypothesis testing (Pérez-Vicente & Expósito Ruiz, 2009:314). Inferential statistics can be classified as either parametric or nonparametric (Allua & Thompson, 2009:168). Parametric statistics is the most common type here and requires that the variables must be measured at the interval or ratio level, whereas nonparametric statistics is used for variables at the nominal or ordinal level of measurement. In contrast with descriptive statistics, inferential statistics can be calculated with the purpose of generalising the findings from a sample to the entire population of interest (Allua & Thompson, 2009:168).

The following inferential statistics is used to analyse the data:

3.7.2.1 Student's *t-test* (*t*)

The student *t-test* is one of the most basic tools of data processing in the scholarly sciences as well as in practice (Fedor-Freybergh & Mikulecky, 2005:170). The *t-test* is valid when

variables are normally distributed, or for variables that can be transformed into normal distribution by using logarithms (Carlin & Doyle, 2001:77). A student's *t-test* investigates whether the expected values for two groups are the same; these tests can be used for paired or unpaired groups (Du Prel *et al.,* 2010:345). A paired *t-test* is used for normal distributed continuous parameters in two paired groups (Carlin & Doyle, 2001:76). The unpaired *t-test* is used where subjects in both groups are independent of each other and the parameters are normally distributed and continuous (Carlin & Doyle, 2001:77). The practical significance of the results is computed when the *p*-value is statistically significant ($p \leq 0.05$) (refer to 3.7.3.1).

The *t-test* is used to determine the influence of gender on the average number of asthma prescriptions per patient per year, the average number of asthma medicine items per prescription and the average cost of asthma medication.

3.7.2.2 ANOVA

An analysis of variance (ANOVA) is slightly more complex than a *t-test* but is based on the same mathematical principles (Allua & Thompson, 2009:169). Although ANOVA can be used with two groups, it is most commonly used for independent variables that have three or more groups (age groups and provinces) (Du Prel *et al.,* 2010:344). ANOVA is statistically calculated as F (Allua & Thompson, 2009:169). With an ANOVA, a statistically significant p-value indicates that there are group differences present in the data, but it does not indicate which groups are different (Allua & Thompson, 2009:169). The practical significance of the results was computed when the *p*-value was statistically significant ($p \leq 0.05$) (refer to 3.7.3.1).

The ANOVA was used to determine the influence of the age group and provinces on the average number of asthma prescriptions per patient per year, the average number of asthma medicine items per prescription and the average cost of asthma medication.

3.7.2.3 Chi-Square test (χ^2)

The chi-square test is a common statistical test used to examine the significance between two (or more) nominal level variables (Du Prel *et al.,* 2010:344).The chi-square test calculates the expected number of observations in each cell of the contingency table and compares them with the number of observations actually occurring in each cell. The χ^2 *is* used to compare

treatment effect or the frequencies of side effect in two treatment groups (Du Prel *et al.,* 2010:344). The practical significance of the results was computed when the *p*-value was statistically significant ($p \leq 0.05$) (refer to 3.7.3.1).

The χ^2 was used to determine possible statistical significant associations between the variables, gender, age groups and provinces, and the prevalence of asthma.

3.7.3 Statistical and practical significance

The following equations were used to compute and interpret the statistical and practical significance in the various situations.

3.7.3.1 *P*-value

The concepts of randomness and probability are central to statistics (Dalgaard, 2008:55). A *p*-value has a range from 0 to 1 and it is the probability of observing the results from a study or when the null hypothesis is true (Pandis 2013:150).

The null hypothesis states that: "*The true difference in the effect of the experimental and control treatment on the outcome of interest is zero"* (Guyatt *et al.,* 1995:28).

A *p*-value of ≤ 0.05 is often used as a cut-off value for deciding whether a result is statistically significant (Donath *et al.,* 2013:18).

In statistical terminology, mistakenly concluding that there is a difference is called a Type I error (Guyatt *et al.,* 1995a:152a). A Type II error occurs when the null hypothesis was accepted when it was actually false (Biau *et al.,* 2009:2286).

The lower the *p*-value, the more unlikely the null hypothesis would be, and at some point of low probability, the null hypothesis should preferably be rejected (Biau *et al.,* 2009:2286). Moreover, statistical significance does not entail a clinically important observation. The size of the effect determines the practically significance, not the p-value (Gupta, 2012:143-144).

The following equations were used to compute and interpret the effect sizes (thus to establish practical significance) in the various situations

3.7.3.2 Effect sizes / *d*-values

The *d*-values are the most sufficiently single statistic method to evaluate the practical significance and to describe the strength of relationship between variables (Maher *et al.,* 2013:350). The formula of effect sizes is given as equation 3.5:

$$d = \frac{\overline{\tilde{x}_a - \tilde{x}_b}}{S_{max}}$$

Equation 3.5: Statistical equation for calculating the d-value (Cohen 1988:26)

Where:

d = Effect size

$\tilde{x}_a$ = Average value of a

$\tilde{x}_b$ = Average value of b

S_{max} = The largest deviation between the two averages

The effect size can be interpreted as follows:

- If the d-value = 0.2 there is no significant difference between the means
- If the d-value = 0.5 there is a slight significant difference between the means
- If the d-value ≥ 0.8 there is a practical difference between the means

3.7.3.3. Cramer's V

Once the statistical significance has been determined with χ^2, Cramer's V can be used to measure the strength of association between data (Acock & Stavig, 1979:1381).

The formula of Cramer's V is given as equation 3.6:

$$v = \sqrt{\frac{\chi^2}{n}}$$

Equation 3.6: Statistical equation for calculating the Cramer's V (Acock & Stavig, 1979:1381)

χ^2 = Chi-square

n = number of sample elements

The results are interpreted according to the following criteria:

- If the Cramer's V -value = 0.1 there is a small effect and the results can be interpreted as non-significant.
- If the Cramer's V -value = 0.3 there is a medium effect and the results may be interpreted as observable, which may reflect on significant differences.
- If the Cramer's V -value = 0.5 there is a large effect and the results can be interpreted as significant and of practical importance (SSC, 2012).

3.8 RELIABILITY AND VALIDITY OF THE RESEACH INSTRUMENTS

The data was, as noted, obtained from a medical claims database. There was no direct involvement or manipulation of the data by any of the researchers. The research was performed with the assumption that all data acquired from the medicine claims database was valid and reliable. The data for analysis was, however, obtained from one medicine claims database only, and therefore external accuracy is limited and the results can only be generalised to the allocated database and a study population that were used in the study.

3.9 ETHICAL CONCERNS

Patients, medical schemes, medical practices and pharmacies could not be identified in this study. There were thus no confidentially breaches. This study was authorised by the Ethics Committee of the North-West University (NWU-00005-07-A5) and the boards of directors of the

PBM. Data privacy and confidentiality were maintained at all times. Thus, no patient data or medical scheme could be traced, and it is not possible to determine which prescriber or provider was involved in the prescribing and dispensing of the medicine items.

3.10 CHAPTER SUMMARY

Describing the various methodologies and research issues related to this study is a multifaceted pursuit. In this chapter, various aspects applicable to the empirical investigation were discussed.

In the following chapter, the results from the empirical study are documented and discussed.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 INTRODUCTION

In this chapter, the results of the empirical study are reviewed and discussed. The prevalence of asthma in a section of the private healthcare sector of South Arica will be explored also considering the cost associated with and COPD in asthma treatment in the population for the study period 1 January 2008 to 31 December 2011. The data was analysed in periods of 12 months each.

The data was scrutinised in terms of number of patients, number of prescriptions, number of items on a prescription and the cost of asthma medication items and prescriptions. The cost implications of COPD as a co-morbidity of asthma were also included in this study for the study period of 1 January 2008 to 31 December 2011.

The medication items were extracted from the total database according to the MIMS$^{@}$ classification system of the active ingredient of each item. Data was only extracted if the prescription matched the ICD-10 coding of asthma (refer to Appendix B). In order to study the cost implications of COPD as co-morbidity, data containing the COPD together with asthma ICD-10 coding (refer to Appendix B) was also extracted from the database.

The literature review indicated that asthma has a substantial prevalence among children; not only globally, but also in South Africa. What is more worrying is that asthma in South Africa has amongst the highest mortality rates in the world (Green, 2011:14). To reiterate, then, the aim of this study was to confirm the prevalence of asthma in South Africa and to identify the prescribing patterns of asthma and asthma with COPD in a section of the private health sector of South Africa. It is hoped that the findings of this study can help to alleviate the effects of asthma on the people and the economy of the country

4.2 TERMS AND DEFINITIONS

A number of terms and definitions need to be explained for the purpose of the current discussion. These include:

4.2.1 The total (total population) and asthma database (study population)

The total database consisted (N) of all prescriptions claimed through the PBM company during 1 January 2008 to 31 December 2011. The asthma database (n) consisted of asthma medicine items on prescriptions claimed by patients who have been diagnosed with asthma and status asthmaticus (ICD-10 coding J46 and J45) according to the Chronic Disease List (CDL) of South Africa. Data that bore the asthma J46 and J45 ICD-10 coding was used to study the prescribing patterns of asthma in this study.

4.2.2 Patient

For the purpose of this study, a patient is a person who is receiving or who is registered to receive medical treatment by an authorised prescriber. The patient is also the person who claims the prescription from a pharmacy.

4.2.3 Prescription

For the purpose of this study, a prescription is defined as a written direction by the medical practitioner to the pharmacist for the preparation and use of a medicine or remedy as stipulated by the Medicines and Related Substance Control Act 101 of 1965. A prescription may consist out of more than one medicine item. For the purpose of this study, prescriptions are indicated with the R_X symbol.

4.2.4 Medicine items

A medicine item is a drug or other preparation used for the treatment or prevention of a disease. These medicine items are written down by the prescriber on the prescription that is dispensed by a pharmacist. The pharmacist or patient may claim the cost of the prescription from the medical scheme of the patient.

4.2.5 Asthma medication

Asthma medication is medication that is associated with the prevention and treatment of asthma. For the purpose of this study, asthma medication includes controllers/anti-asthmatics and relievers/bronchodilators as discussed in Chapter 2.

4.2.6 Age groups

In the context of this study, the patients were divided into different age group groups, the first ranging from 0-7 years (age group 1) for children and the second from > 7- ≤18 years of age (age group 2) for adolescents.

As is the case with paediatric patients, older patients were placed in separate groups. They are defined as persons older than 18 years of each, and this group was further divided into three age groups ranging from > 18 ≤ 45 years (age group 3), 45 ≤ 65 years (age group 4) and 65 years and older (age group 5).

4.2.7 Geographical areas

Geographical areas, as used in this dissertation, are defined as the nine provinces of South Africa, namely Gauteng, KwaZulu-Natal, the North-West Province, the Free State, Western Cape, Eastern Cape, Mpumalanga, Limpopo and the Northern Cape.

4.2.8 Active Ingredient

An active ingredient is the substance in a pharmaceutical drug or pesticide that is biologically active. For purposes of this study, only the active ingredients that were used for the treatment of asthma and COPD were engaged.

4.2.9 Combination products

For the current study, a combination product is defined as one asthma product consisting of two active ingredients, for example budesonide/formoterol. It is classified as one product and should be distinguished from “combinations” or “combination therapy”.

4.2.10 Combinations or combination therapy

A combination or combination therapy can be defined as a two products that are prescribed to a patient in conjunction with each other. Usually an asthma product is prescribed together with another asthma product or corticosteroid.

4.2.11 Cost

For the purpose of this study, cost is defined as the amount spent (measured in South African Rands) to obtain medication. The total and average costs are considered. The total cost includes all costs incurred by the third-party payer as well as by the patient (in the form of levies). The data only includes the medication claim information from this section of the

private health sector of South Africa. Hospitalisation and other treatment costs that impact on the overall cost of asthma were not included.

4.2.12 Generic product

These are products that contain the same active ingredient as the original product, but are not patented as the original product. Generic products are usually cheaper than the original product.

4.3 OVERVIEW OF TOTAL DATABASE

For the purpose of this study, only the medicine items were analysed. Non-medicine items (e.g. needles, plasters, etc.) were excluded from the database.

As mentioned in the problem statement of Chapter 1 (refer to section 1.5.1), the current study focuses on identifying the prescribing patterns of asthma medication in a section of the private health sector in South Africa, and sets out to address the following objectives:

- To determine the prevalence of asthma from the year 2008 to 2011 as stratified by age group, gender and geographical distribution,
- To investigate the influence of gender and age on the prescribing patterns of asthma prescriptions and items according to the database and the cost-implication thereof,
- To determine the medicine costs of treating asthma from the year 2008 to 2011 and the influence of age groups, gender and the cost incurred by the third-party payer as well as by the patient (in the form of levies),
- To determine the generic influence on asthma medication and the cost implication thereof, and
- To investigate the prevalence of COPD in asthma patients and the cost-implications thereof.

Table 4.1 summarises the prevalence and cost of all medicine items on the database for the study period 1 January 2008 to 31 December 2011.

Table 4.1: The general prescribing patterns of the total database for the years 2008 to 2011

Year	Total number of patients	Total number of R_x	Total number of medicine items	Total expenditure on medicine items (R)
2008	974 497	6 775 863	16 439 253	1 785 871 013.85
2009	1 307 528	9 023 205	21 648 991	2 509 210 769.88
2010	1 220 289	8 515 428	20 527 777	2 460 225 810.66
2011	1 077 834	7 371 213	17 766 594	2 010 783 076.00

From table 4.1 it can be seen that the total number of patients, total number of prescriptions, total number of medicine items and total expenditure increased from 2008 to 2009, followed by a decrease in 2010 to 2011 (illustrated in figure 4.1). The increase and/or decrease of the general prescribing patterns can often be associated with membership changes with medical schemes and/or medical scheme contract changes with the specific PBM.

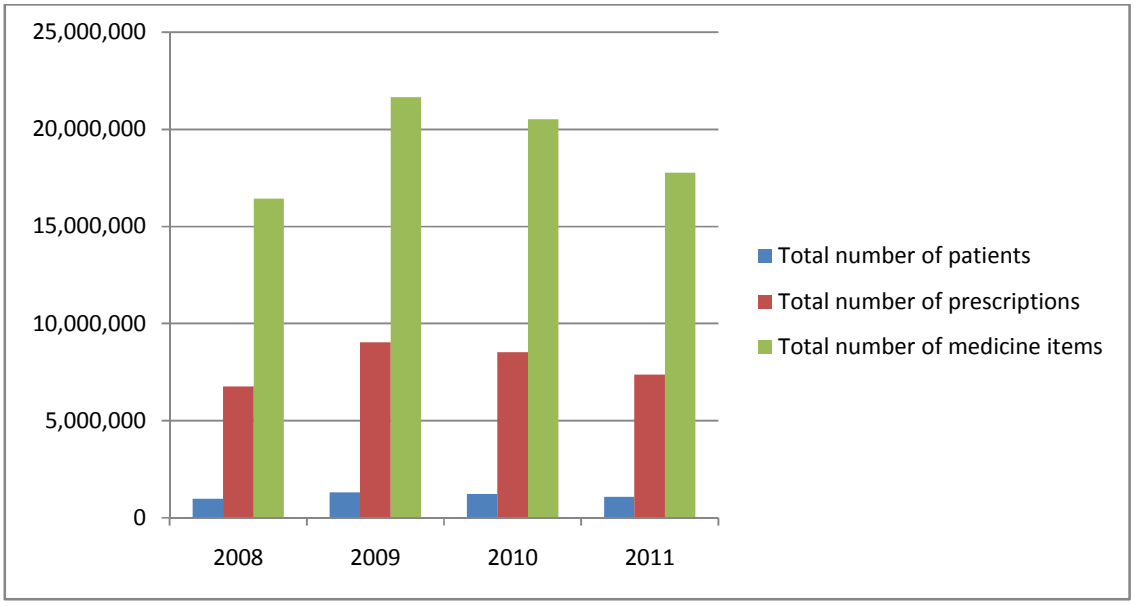


Figure 4.1: General prescribing patterns of the total database

4.3.1 The general prevalence of asthma against the total database

In this section the overall prevalence of asthma will be compared to the total database.

Table 4.2: General prescribing patterns of asthma for the years 2008 to 2011

Year	Total number of asthmatic patients	Total number of asthma R_x	Total number of asthma items	Total cost of asthma items (R)
2008	7 949	65 817	102 167	18 187 239.41
2009	15 423	85 737	110 415	22 599 768.85
2010	13 906	78 122	101 163	21 868 839.74
2011	8 554	44 012	61 395	14 178 449.74

From table 4.3 it can be seen that the percentage of patients who claimed asthma medication showed a steady increase from 2008 [0.82% (n = 7 949, N = 974 497)] to 2009 [1.18% (n = 15 423, N = 1 307 528)]. However, this percentage decreased rapidly (0.39%) from 2010 [1.14% (n = 13906, N = 1 220 289)] to 2011 [0.79% (n = 8 554, N = 1 077 834)]. This decrease may be due to the fact that the total number of patients on the database showed the same increase and decrease over the study period (refer to table 4.1).

Table 4.3: A summary of the prescribing patterns of the asthma database against the total database throughout the study period

Year		Total number of patients	Total number of R_x	Total number of medicine items
2008	**Total database**	974 497	6 775 863	16 439 253
	Asthma database	7 949	65 817	102 167
	% of asthma prevalence*	**0.82**	**0.97**	**0.62**
2009	**Total database**	1 307 528	9 023 205	21 648 991
	Asthma database	15 423	85 737	110 415
	% of asthma prevalence*	**1.18**	**0.95**	**0.51**
2010	**Total database**	1 220 289	8 515 428	20 527 777
	Asthma database	13 906	78 122	1 01 163
	% of asthma prevalence*	**1.14**	**0.92**	**0.49**
2011	**Total database**	1 077 834	7 371 213	17 766 594
	Asthma database	8 554	44 012	61 395
	% of asthma prevalence*	**0.79**	**0.60**	**0.35**

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100

If the prevalence of asthma is studied, the same trends that occurred with the total database can also be seen in the number of asthma items and the number of asthma prescriptions over the four year study period. These increase and decrease of the prescribing patterns of asthma are further discussed in this chapter. The percentage of asthma medicine items and asthma prescription against the total database also showed the same increase (from 2008 to 2009) and decrease (from 2009 to 2011) over the four year study period (Table 4.3).

4.3.2 Medication cost associated with of asthma as a disease

According to Campos and Lemos (2009:305), asthma accounts for substantial expenditures – approximately 1% of all health care cost in most developing countries (Campos & Lemos, 2009:305). Table 4.4 indicates the cost of asthma medication against the total cost of medication in the database. The total cost of asthma medication was analysed per year. Furthermore, only the direct cost of asthma treatment (only medication) was analysed, thus hospitalisation and indirect costs were not included in this study.

Table 4.4: A summary of the total medicine cost of asthma medication against the total medicine cost of the total database

Year	Total cost of medicine items (R)	Total cost of asthma medicine items (R)	% of Total cost*
2008	1 785 871 013.85	18 187 239.41	1.02%
2009	2 509 210 769.88	22 599 768.85	0.90%
2010	2 460 225 810.66	21 868 839.74	0.89%
2011	2 010 783 076.00	14 178 449.74	0.71%

* Asthma cost (%) is calculated by dividing the asthma expenditure by the total expenditure for the specific year multiplied by 100

From table 4.4 it can be seen that the total medication cost of asthma has increased from 2008 (n = R18 187 239.41, N = R1 785 871 013.85) to 2009 (n = R22 599 768.00, N = R2 509 210 769.88). The percentage that it represented from the total cost decreased with 0.12%. The percentage of the total cost then decreased further from 0.89% (n = R21 868 839.74, N = R2 460 225 810.66) in 2010 to 0.71% (n = R14 178 449.74, N = R2 010 783 076.00) in 2011. The asthma expenditures as part of the total expenditure showed a decrease from 2008 to 2011. This could be due to less expensive generic medicine items that were made available during the study period or due to the fact that the overall expenditure decreased from 2008 to 2011 (refer to table 4.19).

The results are basically consistent with the study by Campos and Lemos (2009:305) indicating that asthma accounts for only 1% (0.88%) of the total expenditure in developing countries.

4.4 THE PRESCRIBING PATTERNS OF ASTHMA

The following section focuses on the prescribing patterns of asthma medication. The number of asthma patients, number of prescriptions and medicine items are discussed and will be compared to the total database in order to obtain a clear overview of the management of asthma in South Africa. The influence of geographical areas, gender and age groups on the prescribing patterns of asthma are also investigated and discussed.

4.4.1 The number of asthma patients on the databases

The number of patients who claimed asthma medication showed a steady increase (0.36%) from 2008 [0.82% (n = 7 949, N = 974 497) to 1.18% (n = 15 423, N = 1 307 528)] in 2009, with a slight decrease of 0.04% in 2010 [1.14% (n = 13 906, N =1 220 289) and a further 0.35% decrease in 2011 to 0.79% (n = 8 554, N = 1 077 834)] (refer to table 4.2 and 4.3).

The percentage of asthma patients represented in the total database showed a very low value throughout the four year period with the maximum value of 1.18% (n = 15 423) during 2009 and a minimum value of 0.79% (n = 8 554) in 2011 (refer to table 4.2 and 4.3). These low values of prevalence can be attributed to the fact that this study only investigated chronic asthma medication prescribed to chronic asthma patients registered on the CDL and not asthma medication prescribed on a short-term basis such as acute but non-chronic asthma conditions. The low percentage values can also be attributed to misdiagnoses since many clinicians are confused as to how and if they should differentiate asthma from other obstructive airways disease like COPD (Gibson & Simpson, 2009:729).

4.4.2 The general prescribing patterns of asthma prescriptions on the databases

Table 4.5 indicates the number of asthma prescriptions that were dispensed and claimed through the PBM from 2008 to 2011 compared to the total database.

Table 4.5: The general prescribing patterns of asthma prescriptions against the total database from 2008 - 2011

Year		Total number of R_x	Average R_x per patient per year (SD)	CI 95%
2008	**Total database**	6 775 863	6.95 ± 7.85	
	Asthma database	65 817	8.28 ± 5.47	8.16-8.40
	Prevalence %*	**0.97**		
2009	**Total database**	9 023 205	6.90 ± 7.88	
	Asthma database	85 737	5.56 ± 4.71	5.48-5.63
	Prevalence %*	**0.95**		
2010	**Total database**	8 515 428	6.98 ± 7.89	
	Asthma database	78 122	5.62 ± 4.67	5.54-5.70
	Prevalence %*	**0.92**		
2011	**Total database**	7 371 213	6.84 ± 7.54	
	Asthma database	44 012	5.15 ± 4.12	5.06-5.23
	Prevalence %*	**0.60**		

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100

From table 4.5 it can be seen that total number of prescriptions for asthma patients showed an increase from 2008 (n = 65 817, N = 6 775 863) to (n = 85 737, N = 9 023 205) in 2009, with a decrease in number of prescriptions to (n = 78 122, N = 8 515 428) during 2010 and a further decrease to (n = 44 012, N = 7 371 213) in 2011. This finding correlates with the patterns that emerged in terms of the number of asthma patients on the total database. However, the percentage of asthma prescriptions against the total database decreased with

0.37% from 2008 [0.97% (n = 65 817, N = 6 775 863)] to 2011 [0.60% (n = 44 012, N =737 121 213)].

Furthermore, the average asthma prescription per patient per year decreased significantly during the study period, with a maximum average of 8.28 ± 5.47 prescriptions per year for asthma patients in 2008, followed by a decrease to 5.56 ± 4.71 prescriptions per year in 2009 and 5.62 ± 4.67 prescriptions per year in 2010, hitting an average low of just 5.15 ± 4.12 prescriptions per year for asthma patients during 2011.

For the purpose of this study, only the chronic usage of asthma medications were studied, therefore only patients who were registered for chronic asthma medication or patients using asthma medication for more than three months in a given study year were accounted for, as explained in section 4.4.1. Thus acute asthma prescriptions were not included. This may be a possible reason for the low percentages and the average number of prescriptions per patient.

4.4.3 The general prescribing patterns of asthma medicine items on the databases

Table 4.6 shows the number of asthma medication items in relation to the total number of items on the database. The prevalence as a percentage of asthma items against the total database shows the same trend as the number of asthma prescriptions for all four years (refer to section 4.4.2)

The total number of asthma medication items as a percentage of the total number of medicine items in the total database showed a decrease from 2008 (0.62%), to 2009 (0.51%), but the number of asthma items increased from 102 167 (0.62%, N = 16 439 253) to 110 415 (0.51%, N = 21 658 991). The total number of asthma medications, however, showed a decrease during from 2009 to 2010 (n = 101 163, N = 20 527 777), a trend that continued in 2011 (n = 61 395, N = 17 766 594). However, the prevalence of asthma medicine items against the total database medicine items as a percentage showed a 0.27% decrease in items from 2008 [0.62% (n =102 167 N = 16 439 253)] to 2011 [0.35% n = 61 395, N = 17 766 594)]. These results are summarised in Table 4.6.

Table 4.6: The general prescribing patterns of asthma medicine items against the total database from 2008 - 2011

Year		Total number of medicine items on R_x	Average number of items per R_x (SD)	CI 95%
2008	**Total database**	16 439 253	2.43 ± 1.64	
	Asthma database	102 167	1.55 ± 0.78	1.54 - 1.56
	Prevalence %*	**0.62**		
2009	**Total database**	21 648 991	2.40 ± 1.64	
	Asthma database	110 415	1.37 ± 0.66	1.37 - 1.38
	Prevalence %*	**0.51**		
2010	**Total database**	20 527 777	2.41 ± 1.67	
	Asthma database	101 163	1.38 ± 0.67	1.37 - 1.38
	Prevalence %*	**0.49**		
2011	**Total database**	17 766 594	2.41 ± 1.68	
	Asthma database	61 395	1.39 ± 0.64	1.39 - 1.40
	Prevalence %*	**0.35**		

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100

Regarding the average number of medicine items that appear on a patient's prescription, the total database showed an average of 2 to 3 medicine items per prescription or the four year study period. The asthma database indicated a lower average of 1 to 2 medicine items per prescription in terms of the average number of medicine items for the total database. 2008 was found to have the highest average rate of asthma medicine items per prescription with 1.55 ± 0.78. Furthermore, the years 2009 (1.37 ± 0.66) 2010 (1.37 ± 0.66) and 2010 (1.37 ±0.66) all had the same average number of asthma medicine items per prescription. In a recent study by Mouton (2010:82), the results showed a similar tendency.

Asthma patients do not usually use only one product to treat their asthma (refer to section2.6), as it is more beneficial to use combinations of different medications which also have different purposes when it comes to controlling asthma in patients. Thus these results are in line with the findings of the literature study presented in Chapter 2.

4.4.4 Prevalence of asthma prescribing patterns according to gender

Table 4.7 summarises the prevalence of asthma according to gender in context of the total database.

Table 4.7: A summary of the number of asthma patients against the total database according to gender from 2008 - 2011

Year		Total number of female patients	Total number of male patients
2008	**Total database**	626 708	496 952
	Asthma database	4 574	3 375
	Prevalence %*	**0.73**	**0.68**
2009	**Total database**	844 653	692 732
	Asthma database	9 006	6 417
	Prevalence %*	**1.07**	**0.93**
2010	**Total database**	795 478	660 259
	Asthma database	8 092	5814
	Prevalence %*	**1.02**	**0.88**
2011	**Total database**	705 323	597 104
	Asthma database	4 916	3 638
	Prevalence %*	**0.70**	**0.61**

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100

From table 4.7 it can be seen that there is a clear difference between the number and percentage of female (0.89% n = 26 588, N = 2 972 162) vs. male (0.79% n = 19 244, N = 2 447 047) asthmatic patients. These findings concur with the literature survey where it was found that asthma is more prevalent in females than their male counterparts (Vink *et al.,* 2009:489; Thomas *et al.,* 2010:626). However, the Chi-square test presented a *p*-value of0.41 which translates into the gender difference in terms of the prevalence of asthma patients being not statistical significant ($p > 0.05$) and thus no practical significance can be noted between the number of female and male asthma patients in this section of the private

healthcare sector of South Africa. Next, tables 4.8 and 4.9 summarise the influence of gender on the prescribing patterns of asthma prescriptions and medicine items.

In Table 4.8 the prescribing patterns of asthma items and the influence of female and male patients are presented.

Table 4.8: The prescribing patterns of asthma medicine items in terms of gender from 2008 - 2011

Year	Gender	Total number of asthma Items	Average number of items per R_x (SD)	CI 95%
2008	**Female**	59 233	1.55 ± 0.78	1.54-1.56
	Male	42 934	1.56 ± 0.78	1.55-1.57
2009	**Female**	63 982	1.38 ±0.65	1.37-1.39
	Male	46 433	1.40 ± 0.63	1.38-1.41
2010	**Female**	58 606	1.37 ± 0.66	1.36-1.38
	Male	42 557	1.39 ± 0.69	1.38-1.40
2011	**Female**	34 862	1.39 ± 0.63	1.38-1.39
	Male	26 533	1.41 ± 0.65	1.40-1.42

More asthma medicine items have been prescribed for female patients (n = 216 683) than for their male counterparts (n = 158 457). This trend continued over the four year study period. The average of asthma items per prescription did not differ very much between male and female patients, as seen in table 4.8. The highest average number of items per prescription occurred in 2008 for both female and male patients, which was 1.55 ± 0.78 for female patients and 1.56 ± 0.78 for male patients, respectively. The lowest average number of asthma medicine items per prescription was seen in 2010, with an average of 1.37 ± 0.66 and 1.39 ± 0.63 for female and male patients, respectively. In Table 4.9 the prescribing patterns of asthma prescriptions for female and male patients are summarised. The difference in terms of gender on the prescribing patterns of asthma prescriptions showed no statistical significance ($p > 0.05$.)

Table 4.9: The prescribing patterns of asthma prescriptions between genders from 2008 - 2011

Year	Gender	Total number of asthma R_x	Average number of R_x per patient per year (SD)	CI 95%
2008	**Female**	38 278	8.37 ± 5.50	8.20-8.53
	Male	27 539	8.16 ± 5.42	7.97-8.34
2009	**Female**	49 804	5.53 ± 4.68	5.43-5.63
	Male	35 933	5.60 ± 4.76	5.48-5.48
2010	**Female**	45 474	5.62 ± 4.67	5.51-5.72
	Male	32 648	5.62 ± 4.67	5.49-5.74
2011	**Female**	25 150	5.12 ± 4.10	5.00-5.23
	Male	18 862	5.18 ± 4.12	5.055.32

From table 4.9 it can be seen that the number of prescriptions showed the same trends as asthma patients and asthma medicine items in terms of gender, where females (n = 158 706) had a higher prevalence than male patients (n = 114 982). This trend continued over the four year study period. The number of asthma medicine items on a prescription increased from 2008 to 2009. There was a concomitant decrease for both male and female patients in the number of medicine items per prescription from 2009 to 2011.

The average number of prescriptions per patient per year did not differ very much in terms of male and female patients as seen in table 4.9; however, male patients showed a slightly higher prevalence during 2009 and 2011. The highest average number of prescriptions per patient per year occurred in 2008 for both female and male patients; this number was 8.37 ± 5.50 per year and 8.16 ± 5.42 per year, respectively. The average number of asthma items per prescription showed a decrease throughout the study period. The lowest prevalence of prescriptions for females occurred in 2011 with an average of 5.12 ± 4.10 per year and 5.18 ± 4.12 per year, respectively for males.

4.4.5 Prevalence of asthma prescribing patterns of asthma according to age groups

As stated in the empirical study, the asthma population was divided into five age groups, to determine the influence of different age groups on the prescribing patterns of asthma (refer to Chapter 3, section 3.6.2.2). For the purpose of this section, the age groups were divided into age group 1 (AG1) for children between 0-7 years, age group 2 (AG2) for adolescents between > 7 ≤ 18 years. Adult patients were divided into three groups, namely age group 3 (AG3) for > 18 ≤ 45 years, age group 4 (AG4) for > 45 ≤ 65 years, and age group 5 (AG5) for patients older than 65 years. In table 4.10 the prevalence of asthma according to the different age groups is illustrated in the context of the total database.

Table 4.10: A summary of the number of asthma patients against the total database according to age groups from 2008 - 2011

Year		AG1**	AG2**	AG3**	AG4**	AG5**
2008	**Total database**	70 293	154 484	405 031	353 695	140 157
	Asthma database	394	939	1 565	2 661	2 390
	Prevalence %*	**0.56**	**0.61**	**0.39**	**0.75**	**1.71**
2009	**Total database**	134 081	189 974	585 233	444 713	183 384
	Asthma database	1 134	1 760	3 358	4 944	4 227
	Prevalence %*	**0.85**	**0.93**	**0.57**	**1.11**	**2.30**
2010	**Total database**	128 257	164 370	549 018	425 192	188 900
	Asthma database	892	1 454	2 927	4 601	4 032
	Prevalence %*	**0.70**	**0.88**	**0.53**	**1.08**	**2.13**
2011	**Total database**	117 418	141 789	489 850	374 971	178 403
	Asthma database	489	882	1 773	2 656	2 754
	Prevalence %*	**0.42**	**0.62**	**0.36**	**0.76**	**1.54**

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100.

** AG1: 0 – 7 years, AG2: > 7 ≤ 18 years, AG3: > 18 ≤ 45 years, AG4: > 45 ≤ 65 years, AG5: > 65 years.

Overall, from table 4.10, it could be seen that the prevalence of asthma patients was the highest among adults between the ages of AG4 and AG5. The highest prevalence was seen in 2009 [2.30% (n =4 227, N =183 384)] in AG5, with the lowest prevalence being in 2008 in AG3 (0.36%). Children in AG1 had the highest prevalence of patients (0.85%) in 2009 and among adolescents in AG2 the highest prevalence of patients also occurred in 2009 (0.93% (n = 1 565, N = 405 031). The high asthma prevalence in AG4 and AG5 could be attributed to many factors such as the deterioration of the lungs, co-morbid situations (COPD) and poly pharmacy (aspirin) which are frequently associated with elderly patients (Yorgancioğlu & Sakar Coskun, 2012:81; Hanania *et al.,* 2011:S7).

The data showed a statistical significance association between asthma prevalence and the age groups of this study ($p<0.0001$). The Cramer's V was used to indicate the practical significance of the data (refer Chapter 3, section 3.7.3.3). The Cramer's V showed a value of 0.0314 which can be described as a small effect and as non-significant. Thus, no practical significance was found in terms of the number of asthma patients according to age groups from 2008 to 2011

Table 4.11 to 4.14 indicates the prescribing patterns of asthma with reference to children, adolescents and adults and the influence of age groups for the study period. A brief discussion of each table is also given explaining the trends associated with the age groups.

Table 4.11 indicates that the average number of asthma medicine items per prescription in children and adolescents did not vary much with the maximum average number of asthma items per prescription ranging from 1.56 ± 0.74 in 2008 to 1.40 ± 0.63 in 2009 for children in AG1. Adolescents in AG2 showed an average decrease in prescriptions per year, with 2008 having the highest average rate of prescriptions with 1.56 ± 0.73 and 2009 with the lowest average prescription rate per year (1.40 ± 0.63). The average number of prescriptions per year remained fairly constant with in AG1 and AG2. The total number of medicine items for adolescents (AG2, n = 35 003) was higher than in children (AG1, n = 18 848). This finding could be attributed to the fact that the age bracket was larger for adolescents in AG2 than in children in AG1, of which more patients could be enrolled from in AG2.

Table 4.11: The prescribing patterns of asthma items in children and adolescents from 2008 - 2011

Year	Age group**	Total number of asthma Items	Average number of items on R_x (SD)	CI 95%
2008	**AG1**	4 606	1.56 ± 0.74	1.53-1.58
	AG2	10 355	1.56 ± 0.73	1.55-1.59
2009	**AG1**	6 540	1.41 ± 0.64	1.40-1.43
	AG2	10 233	1.40 ± 0.63	1.38-1.41
2010	**AG1**	5 198	1.41 ± 0.67	1.38-1.43
	AG2	8 995	1.42 ± 0.65	1.40-1.43
2011	**AG1**	2 504	1.40 ± 0.65	1.37-1.43
	AG2	5 420	1.41 ± 0.59	1.37-1.41

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100.

** AG1: 0 – 7 years, AG2: > 7 ≤ 18 years

Table 4.12 shows the average number of asthma medicine items per prescription in adults according to the three different age groups. Adults in AG4 had a higher average number of asthma medicine items prescribed over the four year study period. For AG3, the maximum average 1.59 ± 0.77 occurred in 2008 and the minimum of 1.36 ± 0.63 in 2009. The average number of asthma medicine items prescribed for AG4 ranged from 1.60 ± 0.83 in 2008 to 1.39 ± 0.69 in 2010. The oldest age group, AG5, had a slightly higher average of asthma medicine items on a prescription in 2008 with 1.48 ± 0.75 and the minimum was in 2011 only reaching 1.34 ± 0.61. The average number of items per prescription remained in close proximity with each other with over the study period. The differences in age groups on the average number of prescription per year showed no statistical significance ($p > 0.05$).

Table 4.12: The prescribing patterns of asthma medicine items in adults from 2008 - 2011

Year	Age group**	Total number of asthma items	Average number of items per R_x (SD)	CI 95%
2008	**AG3**	11 860	1.59 ±0.77	1.58-1.61
	AG4	36 428	1.60 ± 0.83	1.59-1.61
	AG5	31 918	1.48 ± 0.75	1.47-1.49
2009	**AG3**	21 433	1.36 ± 0.63	1.39-1.41
	AG4	38 310	1.40 ± 0.68	1.39-1.41
	AG5	33 899	1.34 ± 0.65	1.33-1.35
2010	**AG3**	18 895	1.38 ± 0.65	1.37-1.39
	AG4	35 214	1.39 ± 0.69	1.38-1.40
	AG5	32 861	1.35 ± 0.66	1.34-1.36
2011	**AG3**	12 487	1.43 ± 0.66	1.42-1.44
	AG4	20 888	1.43 ± 0.67	1.42-1.44
	AG5	20 096	1.34 ± 0.61	1.33-1.35

** AG3: > 18 ≤ 45 years, AG4: > 45 ≤ 65 years, AG5: > 65 years.

Table 4.13 indicates the total number of asthma prescriptions, their average number per patient per year with their 95% Confidence interval. Both AG1 and AG2 showed an increase in total number of prescriptions from 2008 to 2009 which then decreased in 2010 and decreased further during 2011. AG2 had the highest number of prescriptions (n = 25 411) with regard to children. The average number of prescriptions per patient per year for AG2 over the four year study period ranged from 7.03 ± 4.64 per patients in 2008 and 4.41 ± 3.80 per patient in 2011. AG1 and AG2's average number of prescriptions per patient per year were in close proximity with each other. Children in AG1 had a lower number of prescriptions (n = 13 917) for the study period and the average number of prescriptions per patient ranged from 7.51 ± 5.34 in 2008 to 3.66 ± 3.25 in 2011.

Table 4.13: The prescribing patterns of asthma prescriptions in children and adolescents from 2008 - 2011

Year	Age group**	Total number of R_x	Average number of R_x per patient per year (SD)	CI 95%
2008	**AG1**	2 960	7.51 ±5.34	6.98-8.04
	AG2	6 604	7.03 ± 4.64	6.74-7.33
2009	**AG1**	5 102	4.50 ± 3.68	4.28-4.71
	AG2	8 011	4.55 ± 3.88	4.37-4.73
2010	**AG1**	4064	4.56 ± 3.82	4.30-4.81
	AG2	6 905	4.78 ± 4.04	4.54-4.96
2011	**AG1**	1 791	3.66 ± 3.25	3.37-3.95
	AG2	3 891	4.41 ± 3.80	4.16-4.66

** AG1: 0 – 7 years, AG2: > 7 ≤ 18 years

Table 4.14 indicates the total number of asthma prescriptions and their average number of prescriptions per patient per year for adults. Table 4.14 indicates that AG5 obtained the second highest number of prescriptions (n = 88 796) and the highest average number of prescriptions per patient per year over the four year study period ranging from 9.05 ± 5.88 prescriptions in 2008 and 5.44 ± 4.31 prescriptions in 2011. For AG3, the average number of prescriptions per patient per year ranged from 7.56 ± 5.04 in 2008 to 4.93 ± 3.95 in 2011. AG4's number of prescriptions per patient per year ranged from 8.57 ± 5.49 in 2008 to 5.49 ± 4.14 in 2011. The average value of prescription per patient for the AG3, AG4 and AG4 remained close to each other for each year over the four year study period.

Table 4.14: The prescribing patterns of asthma prescriptions in adults from 2008 - 2011

Year	Age group**	Total number of R_x	Average number of R_x per patient per year (SD)	CI 95%
2008	**AG3**	11 836	7.56 ± 5.04	7.31-7.81
	AG4	22 794	8.57 ± 5.49	8.36-8.77
	AG5	21 623	9.05 ± 5.88	8.81-9.28
2009	**AG3**	16 685	4.97 ± 4.21	4.83-5.11
	AG5	29 195	5.91 ± 4.92	5.77-6.04
	AG4	26744	6.33 ± 5.20	6.17-6.48
2010	**AG3**	14 505	4.96 ± 4.12	4.80-5.10
	AG4	26 845	5.83 ± 4.79	5.70-5.97
	AG5	25 803	6.40 ± 5.11	6.24-6.57
2011	**AG3**	8 751	4.93 ± 3.95	4.75-5.12
	AG4	14 593	5.49 ± 4.14	5.34-5.65
	AG5	14 986	5.44 ± 4.31	5.28-5.60

** AG3: > 18 ≤ 45 years, AG4: > 45 ≤ 65 years, AG5: > 65 years.

From tables 4.13 and 4.14 one can see that adults received a slightly higher average number of prescriptions per patient per year, with AG5 showing the highest average of 9.05 ± 5.88 in 2008. AG1 had the lowest average number of prescription per patient per year claimed, of just 3.66 ± 3.25 in 2011. This finding is quite disturbing because asthma is a serious health problem among children (refer to section 2.2.3). Also, AG4 had the largest number of prescriptions for the study period (n = 93 427) while AG1 had the smallest (n = 13 917) number of prescriptions over the study period. However, this is probably the case because AG4 covered a larger age bracket than AG1, thus AG4 has more patients who received prescriptions.

4.4.6 Geographical distribution of asthma patients in South Africa

South Africa is divided into nine different provinces each with its own fairly distinct population groups, economy, landscape and climate. This section focuses on the influence of geographical area in the prevalence of asthma patients in a section of private healthcare sector of South Africa. Table 4.15 illustrates the percentage prevalence of asthma patients against the total database according to the nine provinces.

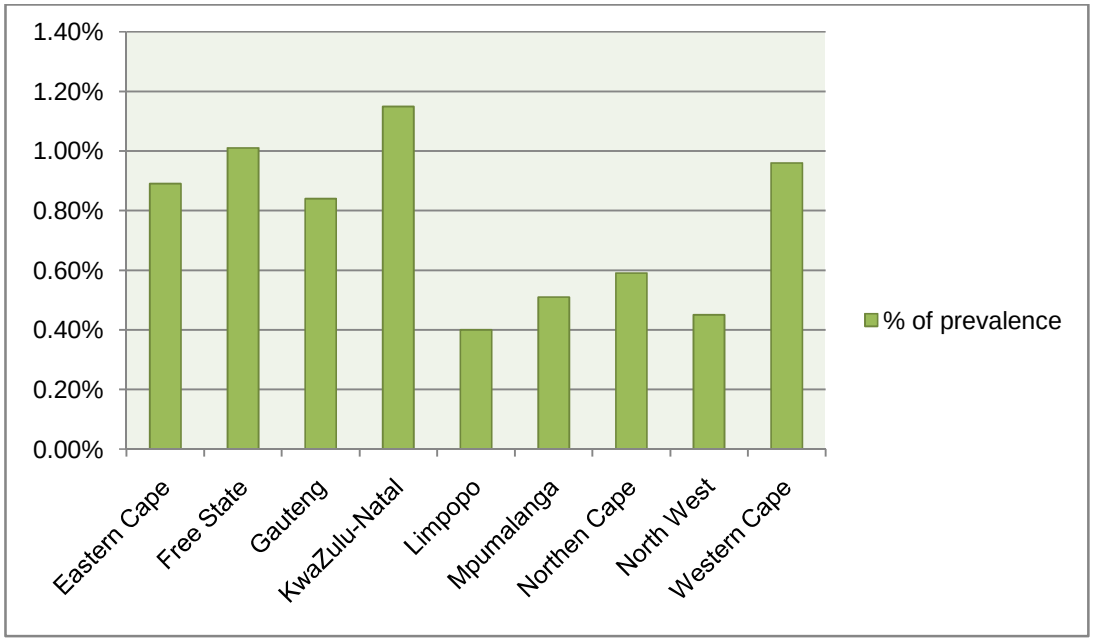


Figure 4.2: Prevalence of the number of asthma patients in percentages.

Although Gauteng had the largest number of patients claiming asthma medication (Table4.15), this province did not have the highest prevalence [0.85% (n = 17 696, N = 2 071 189)] in this section of the private healthcare sector of South Africa. The three provinces with the highest *number* of asthma patients were: Gauteng (n = 17 696) followed by KwaZulu-Natal (n = 8 628) and the Western Cape (n =8 513), as illustrated in figure 4.3. The *prevalence* of asthma against the total database shows a different order, with KwaZulu-Natal [1.16% (n = 8 628, N = 742 499)] having the highest prevalence of asthma patients followed by the Free State [1.03% (n = 2 584, N = 250 822)] and the Western Cape [0.97% (n = 8 513, N = 879 264)] respectively, while Gauteng was fifth after the Eastern Cape [0.90% (n = 3 048, N = 336 840) over the four year study period (refer to figure 4.2).

The reason behind the high number of asthma patients in the top three provinces could be the effect of urbanisation and pollutants (refer to section 2.4.2.2), because Gauteng (Johannesburg/Pretoria), the Western Cape (Cape Town) and KwaZulu-Natal (Durban) are home to South Africa's largest metropolitan centres. However, it is difficult to determine the effect of urbanisation, because pollutants may be found in rural as urbanized areas. Also, provinces like the Western Cape, KwaZulu-Natal and the Eastern Cape are in close proximity to the ocean, which creates the perfect climate for mould, another risk factor for asthma (refer to section 2.4.2.1). The Free State is also a province with a high asthma percentage and this could be ascribed to the long grass pollen period characteristic of South Africa (refer to section 2.4.2.2). More extensive studies should be undertaken to determine the specific causes of asthma in these provinces.

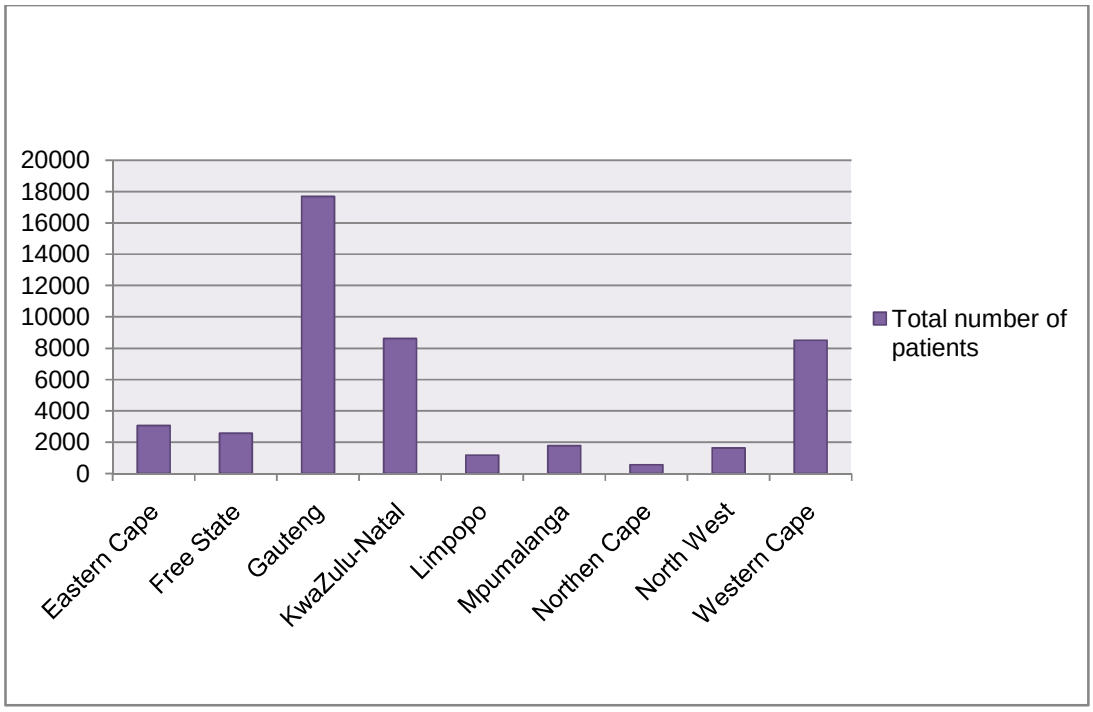


Figure 4.3 **Prevalence of the number of asthma patients.**

The data showed a statistical significance in terms of the different provinces and the number of asthma patients ($p < 0.0001$). The Cramer's V was used to determine the practical significance of the data (refer Chapter 3, section 3.7.3.3). The Cramer's V showed a value of 0.0308 which can be interpreted as a small effect in the differences in number of asthma patients in different provinces. This indicates that the results are classified as non- significant.

Table 4.15: A summary of the number of asthma patients against total database according to geographical areas from 2008 - 2011

Year		Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape
2008	**Total database**	73 915	50 691	419 515	172 707	81 145	70 077	19 325	74 862	154 613
	Asthma database	485	458	2 992	1 531	261	308	110	303	1 483
	% prevalence of that year	**0.66**	**0.90**	**0.71**	**0.89**	**0.32**	**0.44**	**0.57**	**0.40**	**0.96**
2009	**Total database**	97 596	69 281	595 224	21 6921	79 271	94 250	24 279	99 248	246 072
	Asthma database	1 024	873	6 071	2 775	404	631	168	610	2 783
	% prevalence of that year	**1.05**	**1.26**	**1.02**	**1.28**	**0.51**	**0.67**	**0.69**	**0.61**	**1.13**
2010	**Total database**	90 320	69 193	557 599	190 243	69 147	92 429	25 978	94 644	248 700
	Asthma database	973	771	5 391	2 559	317	542	175	496	2 585
	% prevalence of that year	**1.08**	**1.11**	**0.97**	**1.35**	**0.46**	**0.59**	**0.67**	**0.52**	**1.04**
2011	**Total database**	75 010	61 657	498 856	162 628	60 930	89 055	24 831	82 870	229 879
	Asthma database	566	482	3 242	1 763	182	296	101	224	1 662
	% prevalence of that year	**0.75**	**0.78**	**0.65**	**1.08**	**0.30**	**0.33**	**0.41**	**0.27**	**0.72**

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by

4.4.7 The classification of medication cost into third-party payer as well as the patient (in form of levies) from 2008 t0 2011

PBMs are a feature of the Medical Schemes Act no 131 of 1988, in which the medical schemes have to cover the cost related to diagnoses, treatment and care of:

- any emergency medical condition;
- a limited set of ± 270 medical conditions;
- and 27 chronic conditions (defined in the CDL of which asthma is listed) (CMS, 2013b).

Table 4.16 summarises the cost associated with medical aids schemes and patients' cost contribution

Table 4.16: A summary of the total asthma medication cost classified according to levies and third-party payers (medical schemes) from 2008 - 2011

Year	Total cost (R)	Levy* (R)	Scheme amount (R)	Scheme amount as % of total cost
2008	18 187 239.41	148 501.11	15 363 397.44	84.47%
2009	22 599 768.65	245 054.97	18 607 011.30	82.33%
2010	21 868 839.74	474 957.33	18 236 661.75	83.39%
2011	14 178 449.74	946 956 80	12 624 959.22	89.04%

* Amount paid by member

According to the Council for Medical Schemes (CMS) a medical scheme is compelled to cover the total treatment cost of a patient (including medicine cost, doctors' consultation fees, etc.) suffering from one of the 27 diseases listed on the CDL (refer to Appendix B). It is clear from table 4.16, however, that not all medication costs were covered by the medical scheme. These levies are usually paid by the patient if the PMB Company regards medication as too expensive if a cheaper generic equivalent is available (CMS, 2013b).

4.4.8 The cost of asthma prescription and medicine items

As discussed in section 4.2.2 of this chapter, the total cost of asthma increased from 2008 to 2009 and then decreased from 2010 to 2011. However, in table 4.17 it is shown that the average cost per prescription per patient increased throughout the study period, ranging from R276.33 ± R199.86 in 2008 to R322.12 ± R187.59 in 2011. This represents a 14.25% increase in the average cost over the four year study period – a situation that may also contribute to the high prevalence of asthma cost.

Table 4.17: The cost of asthma prescriptions from 2008 - 2011

Year	Total cost of asthma R_x (R)	Average cost of R_x	95% CI (R)
2008	18 187 239.41	276.33 ± 199.86	274.80 - 277.86
2009	22 599 768.65	263.46 ± 205.49	262.08 - 264.84
2010	21 868 839.74	279.80 ± 219.20	278.27 - 281.34
2011	14 178 449.74	322.12 ± 187.59	320.37 - 323.87

Table 4.18 indicates the prescribing cost of asthma prescriptions according to patients' levies. The total cost of levies only contributed 15.62% (n = R12 002 268.03; N = R76 834 297.74) of the total medicine cost. The average levy cost of a prescription per year ranged from R35.29 ± 59.45 in 2011 and R46.47 ± R82.66 in 2009 for this study. These levies are usually paid by the patient if the medical scheme regards medication as too expensive and where a cheaper generic equivalent is available (CMS, 2013b).

Table 4.18: The cost of asthma prescriptions according to levies paid from 2008 - 2011

Year	Total cost of asthma R_x (R)	Average cost of asthma R_x per patient (SD) (R)	95% CI (R)
2008	2 823 841.97	42.90 ± 77.34	42.31 - 43.49
2009	3 992 757.55	46.54 ± 82.66	45.99 - 47.10
2010	3 632 177.99	46.47 ± 85.43	45.87 - 47.07
2011	1 553 490.52	35.29 ± 59.45	34.73 - 35.85

Table 4.19 indicates the asthma prescription cost per patient incurred by the third-party payer (medical schemes). The medical scheme contribution represented 84.38% (n = R64 832 029.27; N = R76 834 297.74) of the total asthma medicine cost for the four year study period. This indicates that the medical scheme was the single highest entity responsible of payment for the cost associated with asthma medication in this section of the private healthcare sector of South Africa. The average cost ranged from R216.91 ± R184.73 per prescription in 2009 to R286.82 ± R170.92 per prescription in 2011.

Table 4.19: The cost of asthma prescriptions according to medical schemes contributions from 2008 - 2011

Year	Total cost of asthma R_x (R)	Average cost of asthma R_x per patient (SD) (R)	95% CI (R)
2008	15 363 397.44	233.42 ± 175.14	232.09 - 234.76
2009	18 607 011.30	216.91 ± 184.73	215.67 - 218.15
2010	18 236 661.75	233.33 ± 197.81	231.94 - 234.71
2011	12 624 959.22	286.82 ± 170.92	285.22 - 288.42

Tables 4.20 – 4.22 present the cost of asthma medicine items and also the cost associated with levies and third party payer for the study period.

Table 4.20: The cost of asthma medicine items from 2008 - 2011

Year	Total cost of asthma medicine items (R)	Average cost of asthma medicine item per R_x (SD) (R)	95% CI (R)
2008	18 187 239.41	178.01 ± 131.91	177.20 - 178.82
2009	22 599 768.65	204.68 ± 156.59	203.76 - 205.60
2010	21 868 839.74	216.17 ± 164.54	215.16 - 217.19
2011	14 178 449.74	230.94 ± 140.88	229.82 - 232.05

The cost of asthma medicine items is summarised in table 4.20. There was a continuous increase in the average cost of medicine items throughout the study period. The year 2008 showed the lowest average cost per asthma medicine items ranging from R178.01 ± R131.91 per asthma medicine item to an average cost of R230.94 ± R140.88 per asthma item in 2011.

Tables 4.21 – 4.22 indicate the cost of asthma medicine items according to levy cost per asthma item and cost incurred by the third party or a medical scheme per medicine item. The average levy cost per asthma medicine item ranged from R25.30 ± R45.96 per asthma item in 2011 and R36.16 ± R65.70 per asthma item in 2009 for as indicated in table 4.21. The total cost of levies represented 15.62% (n = R12 002 268.03, N = R76 834 297.13) of the total asthma medicine cost for the four year study period. As noted, these levies are usually paid by the patient if the medical scheme regards the asthma medication as too expensive and when a cheaper generic equivalent is available (CMS, 2013b).

Table 4.21: The levy cost of asthma items from 2008 - 2011

Year	Total cost of asthma medicine items(R)	Average cost of asthma medicine item per R_x (SD) (R)	95% CL (R)
2008	2 823 841.97	27.63 ± 53.34	42.31 - 43.49
2009	3 992 757.55	36.16 ± 65.70	45.99 - 47.10
2010	3 632 177.99	35.90 ± 67.59	45.87 - 47.07
2011	1 553 490.52	25.30 ± 45.96	34.73 - 35.85

Table 4.22 indicates the third party's contribution to the cost of asthma medicine. The results show that the average medical scheme contribution ranged from R150.37± R119.13 per asthma item in 2008 to a avenge contribution of R205.63 ± R128.81 per item in 2011. This finding indicates that the average cost of an asthma medicine item paid by the medical scheme has increased throughout the study period, and was higher than the levy cost per asthma medicine item.

Table 4.22: Medical scheme contribution of asthma items cost from 2008 - 2011

Year	Total cost of asthma medicine items(R)	Average cost of asthma medicine item per R_x (SD) (R)	Standard error	95% CL (R)
2008	15 363 397.44	150.37 ± 119.13	0.37	149.64 - 151.10
2009	18 607 011.30	168.51 ± 142.15	0.43	169.35 - 169.35
2010	18 236 661.75	180.27 ± 150.09	0.47	179.34 - 181.19
2011	12 624 959.22	205.63 ± 128.81	0.52	204.61 - 206.65

4.4.9 The cost of asthma items according to generic indicators and the cost savings thereof with generic substitution

As medicine costs continue to rise, many public and private payers are upping insurance restrictions and patient cost-sharing for prescribed drugs (Fung *et al.,* 2008:2). Furthermore, many governments are implementing generic medicine policies in the hope of improving access to affordable medicines (Patel *et al.,* 2012:1). Motola and De Ponti (2006) define a generic product as a medicinal item that has the same composition in terms of the active ingredient, the same pharmaceutical from, and being bioequivalent to the original product with regard to safety and efficacy (Motola & De Ponti, 2006:560). Table 4.23 summarises a number of generic and original asthma medicines as well as a number of items with no generic equivalent availability. The prevalence percentage and cost percentage were also calculated, as were the CPI and *d*-values (refer to section 3.7.3.1 in Chapter 3). For the purpose of this study, **original** asthma products are represented by "**O**", the **generic equivalent** of the original product is indicated by an "**Y**" and the asthma products **without** a generic equivalent are indicated by an "**N**".

Table 4.23 shows that during the four year study period, asthma products with no generic equivalent (indicated as "N") had the highest prevalence and accounted for approximately 54.49% (n = 38 4611; N = 705 831) of all medicine items prescribed over this period. However, the total cost percentage was even higher than the percentage prevalence amounting to 78.62 % (n = R114 647 490.90 N = R145 815 501.70) against the total generic indicator database. The highest cost and prevalence for asthma items without a generic equivalent "N" also showed the highest average cost per item ranging from R257.97 ± R115.93 in 2008 to R310.79 ± R121.19 in 2011. The N indicator average cost per item has increased throughout the study period.

The generic asthma medicine (indicated as "Y") was the second most prevalent group and showed a prevalence of 37.45% (n = 264 329; N = 705 831) over the four year study period. This finding could be attributed to the possibility of greater awareness of generic medicine among patients and health care providers, and also by the trend among medical schemes to make generic substitution mandatory. Nonetheless, the total cost of these generic asthma items was approximately 14.11% (n = R20 583 145.11, N = R145 815 501.70) over the four year study period ranging from 10.55% (n = R59 145 83.63, N = R56 057 085.73) in 2009 to 32.44% (n = R4 599 065.06 N = R14 178 449.38) in 2011. The generic asthma medicine items also had the lowest average cost per asthma medicine item over the four year study

period when compared to the other generic indicators ranging from R60.24 ± R68.71 in 2009 to R157.72 ± R116.86 per medicine item in 2011.

The original asthma items had the lowest prevalence both in terms of medicine item and cost. The prevalence of asthma medicine items were 8.06% (n = 56 891; N = 70 5831) and the cost associated with original asthma items reached 7.26% (n = R10 584 865.73 N = R145 815 501.70) against the total asthma generic database over the four year study period. The average cost of an original item ranged from R115.76 ± R115.22 in 2009 to 264.37 ± 135.53 in 2011.

The CPI shows whether if a drug was expensive or inexpensive (refer to Chapter 3 section 3.6.3.3). Table 4.19 indicates that asthma products with no generic equivalent are relatively expensive and for these the CPI was more than 1 throughout the study period, ranging from 1.3 in 2011 to 1.5 in 2009. However, the generic asthma medicine was relatively inexpensive according to the CPI, which is less than 1 throughout the study period. The original items also varied from inexpensive in 2008 (0.8) and 2009 (0.6), reaching an equilibrium in terms of prevalence and cost in 2010 (1.0) and becoming relatively expensive 2011 (1.1).

There was statistically significant (p<0.0001) difference between the avenge cost of items of original and generic asthma medicine items. These differences had a medium to high effect and may be practically significant because the *d-values* ranged from 0.50 in 2009 to 1.19 in 2010 over the four year study period.

Table 4.23: The prescribing patterns and costs of asthma medicine items according to generic indicators from 2008 - 2011

Year	Generic indicator	Number of items	Average cost per item (R)	Total cost (R)	Prevalence %	Cost %	CPI
2008	N	52 954	257.97 ± 115.93	13 660 496.47	51.83	75.11	1.4
	O	8 805	149.64 ± 106.45	1 317 609.92	8.62	7.24	0.8
	Y	40 408	79.42 ± 75.12	3 209 133.02	39.55	17.65	0.4
2009	N	161 191	299.32 ± 131.53	48 247 035.70	58.45	86.07	1.5
	O	16 373	115.76 ± 115.22	18 95 466.40	5.94	3.38	0.6
	Y	98 188	60.24 ± 68.71	5 914 583.63	35.61	10.55	0.3
2010	N	147 687	309.17 ± 133.52	45 660 493.59	55.41	79.56	1.4
	O	22 257	218.89 ± 175.50	4 871 870.26	8.35	8.49	1.0
	Y	96 573	71.04 ± 91.66	6 860 363.40	36.24	11.95	0.3
2011	N	22 779	310.79 ± 121.19	7 079 465.17	37.10	49.93	1.3
	O	9 456	264.37 ± 135.53	2 499 919.15	15.40	17.63	1.1
	Y	29 160	157.72 ±116.86	4 599 065.06	47.50	32.44	0.7

The generic items had a lower average cost per item than the original items. This means that large cost savings are possible through generic substitution; this is further discussed in table 4.24. These savings were calculated by multiplying the number of original items by the average cost of the generic items for each year. This total was then subtracted from the original total cost, and all this data is summarised in table 4.24

Table 4.24: The possible cost savings due to generic substitution on asthma medicine items from 2008 - 2011

Year	Generic indictor	Number of items	Average cost (R)	Total cost (R)	New total cost (R)*	Possible savings (R)
2008	**O**	8 805	149.64 ± 106.45	1 317 609.92	699 293.10	618 315.92
	Y	40 408	79.42 ± 75.12	3 209 133.02		
2009	**O**	16 373	115.76 ± 115.22	1 895 466.40	986 309.52	909 156.88
	Y	98 188	60.24 ± 68.71	5 914 583.63		
2010	**O**	2 2257	218.89 ± 175.50	4 871 870.26	1 581 137.28	3 290 732.98
	Y	96 573	71.04 ± 91.66	6 860 363.40		
2011	**O**	9 456	264.37 ± 135.53	2 499 919.15	1 491 400.32	1 008 518.83
	Y	29 160	157.72 ±116.86	4 599 065.06		

* The new total cost was calculated by multiplying the number of original items per year with the average cost per corresponding year for generic medicine items

From table 4.24 it emerges that the possible cost saving for 2008, if generic substitution were used instead of the original asthma product, could have amounted to R618 315.82 (46.97%, N = R1 317 609.02). In 2009, the generic substitution could have saved R909156.88 (47.96%, N = R1 895 466.40). In 2010, generic substitution could have achieved a 67.55% cost saving (n = R3 290 732.98, N =R 4 8718 70.26). Finally, in 2011 generic substitution could have saved asthma patients R1 008 518.83 (0.40%; N = R2 499 919.15).

4.4.10 The cost of asthma medicine items and prescriptions according to gender

Table 4.25 summarises the influence of gender on the prescribing cost of asthma. It was found that female asthma expenditure (n = R37 192 057.06) was larger than their male counterparts (n = R23 708 240.68). The total cost for female patients ranged from R13 065 532.63 in 2009 to R8 169 940.58 in 2011, while the total cost for male asthma patients ranged from R9 534 236.22 in 2009 to R6 008 509.16 in 2011. These are similar trends as those discussed in section 4.3 an increase was found from 2008 to 2009 of total cost and then a decrease from 2009 to 2011. A possible reason for this difference in total cost in terms of gender can be ascribed to the fact that there were more female asthmatic patients than male asthmatic patients on the database during the four year study period.

Table 4.25: A summary of total asthma medicine cost between genders

Year		Total cost of asthma in female patients (R)	Total cost of asthma in male patients (R)
2008	**Total database**	1 057 274 454.00	728 596 560.20
	Asthma database	10 633 512.52	7 553 726.89
	Prevalence %*	**1.00**	**1.04**
2009	**Total database**	1 460 708 720.00	1 048 502 050.00
	Asthma database	13 065 532.63	9 534 236.22
	Prevalence %*	**0.89**	**0.91**
2010	**Total database**	1 429 235 328.00	1 030 990 482.00
	Asthma database	12 676 071.33	9 192 768.41
	Prevalence %*	**0.89**	**0.89**
2011	**Total database**	1 143 593 475.00	867 189 285.10
	Asthma database	8 169 940.58	6 008 509.16
	Prevalence %*	**0.71**	**0.69**

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100

Tables 4.26 and 4.27 summarise the difference in average cost per prescription and average cost per item between female and male asthmatic patients.

According to table 4.26 there is a clear decrease in the average cost per prescription from 2008 to 2009 and then an increase from 2009 to 2011 for both female and male asthma patients.

In table 4.26 the average cost per prescription for female and male asthmatic patients with their CI 95% intervals is summarised. From table 4.26 a clear decrease in the average cost

per prescription from 2008 to 2009 can be seen, and then an increase follows from 2009 to 2011 for both female and male patients.

For females, the average cost per prescription ranged from R262.19 ± R207.00 in 2009, to R324.81 ± R190.44 in 2011. The average cost per prescription for males ranged from R265.23 ± R203.37 in 2009, to R318.53 ± R183.67 in 2011. Thus, the changes in the average cost per prescription for female and male patients remained consistent with each other over the four year study period.

Table 4.26: The cost of asthma prescriptions according to the gender of patients from 2008 - 2011

Year	Gender	Total cost of asthma R_x (R)	Average cost of R_x per patient (SD) (R)	CI 95% (R)
2008	**Female**	10 633 512.52	277.80 ± 203.18	275.76 - 279.83
	Male	7 553 726.89	274.29 ± 195.12	271.99 - 276.60
2009	**Female**	13 065 532.63	262.19 ± 207.00	260.37 - 264.00
	Male	9 534 236.22	265.23 ± 203.37	263.13 - 267.33
2010	**Female**	12 676 071.33	278.64 ± 221.05	276.60 - 280.67
	Male	9 192 768.41	281.43 ± 216.59	279.07 - 283.77
2011	**Female**	8 169 940.58	324.81 ± 190.44	322.46 - 327.16
	Male	6 008 509.16	318.53 ± 183.67	315.91 - 321.15

Table 4.27 indicates the average cost per asthma medicine item for female and male asthma patients. There is a marked increase in the average cost per medicine item from 2008 to 2011 for both female and male patients. For female patients, the average cost per asthma medicine item ranged from R179.52 ± R131.65 per patient in 2008 to R234.35 ± R208.21 per patient in 2011. The average cost per medicine item for male patients ranged from R175.94 ± R149.96 in 2008 to R226.45 ± R202.25 in 2011.

The change in the average cost per asthma item among female and male asthma patients remained consistent with each other over the four year study period. Thus there were no statistically significant differences in the average cost of asthma items and asthma prescription cost between male and female asthma patients.

Table 4.27: The cost of asthma medicine items according to gender of a patient from 2008 - 2011

Year	Gender	Total cost of asthma R_x (R)	Average cost of asthma medicine item per R_x (SD) (R)	CI 95% (R)
2008	**Female**	10 633 512.52	179.52 ± 131.65	178.46 - 180.58
	Male	7 553 726.89	175.94 ± 149.96	174.69 - 177.19
2009	**Female**	13 065 532.63	204.21 ± 167.47	202.99 - 205.43
	Male	9 534 236.22	205.33 ± 169.96	203.92 - 206.75
2010	**Female**	12 676 071.33	216.29 ± 180.03	214.95 - 217.63
	Male	9 192 768.41	216.01 ± 180.60	214.46 - 217.56
2011	**Female**	8 169 940.58	234.35 ± 208.21	232.86 - 235.84
	Male	6 008 509.16	226.45 ± 202.25	224.78 - 228.12

4.4.11 The cost of asthma medication items and prescriptions according to age groups

Table 4.28 and figure 4.4 indicate the influence of age on the medicine cost of asthma treatment in this study between the year 2008 and 2011.

Table 4.28: A summary of the total asthma medicine cost between age groups from 2008 - 2011

Year		Cost of asthma in AG1** (R)	Cost of asthma in AG2** (R)	Cost of asthma in AG3** (R)	Cost of asthma in AG4** (R)	Cost of asthma in AG5** (R)
2008	**Total database**	36 702 970.85	81 689 724.88	385 100 704.60	721 114 039.60	561 263 573.90
	Asthma database	864 073.46	1 806 567.82	3 928 440.79	6 312 973.89	5 905 183.55
	Prevalence %*	**2.35**	**2.21**	**1.02**	**0.87**	**1.05**
2009	**Total database**	77 826 291.88	108 292 908.76	543 158 151.10	985 607 408.36	794 326 009.78
	Asthma database	1 447 297.39	2 231 598.28	4 380 263.39	7 541 007.87	6 999 601.92
	Prevalence %*	**1.86**	**2.06**	**0.80**	**0.76**	**0.88**
2010	**Total database**	73 819 388.42	97 269 380.38	521 814 594.70	965 479 279.36	801 843 167.80
	Asthma database	1 169 581.41	2 104 373.34	4 107 105.99	7 314 826.33	7 172 952.67
	Prevalence %*	**1.58**	**2.16**	**0.78**	**0.75**	**0.89**
2011	**Total database**	54 047 282.77	70 454 527.97	405 600 493.20	780 414 971.90	700 265 800.40
	Asthma database	622 552.21	1 263 699.31	2 941 583.22	4 727 121.57	4 623 493.43
	Prevalence %*	**1.15**	**1.79**	**0.72**	**0.60**	**0.66**

* Prevalence (%) of asthma is calculated by dividing the asthma databases by the total databases for the specific year multiplied by 100.

** AG1: 0 – 7 years, AG2: > 7 ≤ 18 years, AG3: > 18 ≤ 45 years, AG4: > 45 ≤ 65 years, AG5: > 65 years.

Table 4.28 indicates that the AG4 [0.75% (n = R25 895 929.66, N = R345 261 599.00)] and AG5 [0.86% (n = R24 701 231.57, N = R2 857 698 552.00] had the lowest total asthma expenditures against the total database for all five age groups. AG1 [1.69% (n = R41 035 040.47, N = R242 395 933.90)] and AG2 [2.07% (n = R7 406 238 075, N = R357 706 542.00)] showed the highest asthma expenditures against the total database for all five age groups. =This could be attributed to that asthma occurs in children and adolescents and gradually decreases after adolescence (refer to section 2.3.2).

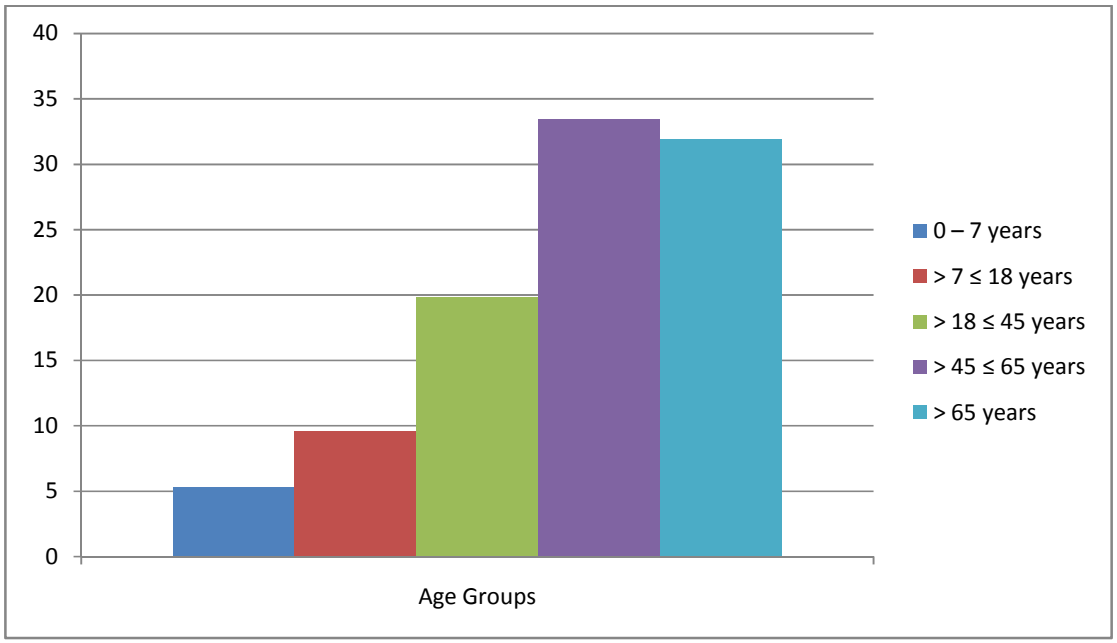


Figure 4.4: Asthma medicine cost as a percentage according to the different age groups.

From figure 4.4, one can conclude that adults in AG4 [33.70% (n = R25 895 929.66; N = R76 834 297.74)] and AG5 [32.15% (n= R24 701 231.57; N = R76 834 297.74)] incurred the highest asthma expenditures. Children had the lowest asthma expenditure for the study period 5.34% (n = R41 035 04.05; N = R76 834 297.74), but this could be attributed to the smaller age bracket in which children were placed, which meant fewer patients. Tables 4.29 and 4.30 present the average cost per asthma prescription in children (AG1), adolescents (AG2) and adults (AG3, AG4, AG5), while tables 4.21 and 4.32 show the average cost per asthma medicine item for the different age groups.

As was the case with the general prescription cost of an asthma prescription, there was an increase from 2008 to 2009 followed by a decrease from 2010 to 2011 for both children and adolescents in AG1 and AG2. For AG1, the highest average cost per prescription occurred in 2011 (R347.60 ± R181.09), with 2009 being the lowest (R283.39 ± R205.63). AG2 also showed the same trend as age group one but with lower cost averages that ranged from R273.55 ± R188.32 per prescription in 2008, to R324.77 ± R184.49 per prescription in 2011. This higher average could be due to the fact that asthma patients used more expensive medicine to treat the disease, or because there was no generic substation available.

Table 4.29: Asthma prescriptions cost in children and adolescents from 2008 - 2011

Year	Age group**	Total cost of asthma R_x (R)	Average cost of R_x per patient (SD) (R)	CI 95% (R)
2008	**AG1**	864 073.46	291.92 ± 200.47	284.69 - 299.14
	AG2	1 806 567.82	273.55 ± 188.32	269.13 - 278.09
2009	**AG1**	1 447 297.39	283.39 ± 205.63	277.75 - 289.03
	AG2	2 231 598.28	278.42 ± 206.93	273.89 - 282.95
2010	**AG1**	1 169 581.41	287.79 ± 213.69	281.21 - 294.36
	AG2	2 104 373.34	304.62 ± 223.08	299.36 - 309.89
2011	**AG1**	622 552.21	347.60 ± 181.09	339.20 -355.99
	AG2	1 263 699.31	324.77 ± 184.49	318.97 – 330.57

** AG1: 0 – 7 years, AG2: > 7 ≤ 18 years.

The same trend that was seen among children and adolescents was also prevalent in the three age groups of adults where there was a decrease in average cost of an asthma prescription from 2008 to 2009, followed by an increase in the cost of an asthma prescription in 2010 to 2011. AG3 showed the highest average cost of prescriptions among adults, with the average cost per prescription ranging from R262.41 ± R209.94 in 2009, to R336.14 ± R186.03 in 2011. AG4 showed a lower average cost per asthma prescription than AG3 (R258.13 ± R204.75 in 2009, and R323.86 ± R192.54 in 2011). AG5 incurred an average

cost of a prescription lower than AG3 and AG4 with the average cost per prescription reaching R262.41 ± R209.94 in 2009, to R308.50 ± R192.54 in 2011.

Table 4.30: Asthma prescription cost in adults from 2008 - 2011

Year	Age group**	Total cost of asthma R_x (R)	Average cost of R_x per patient (SD) (R)	CI 95% (R)
2008	**AG3**	3 928 440.79	278.68 ± 196.06	275.14 - 282.21
	AG4	6 312 973.89	276.96 ± 209.39	274.23 - 279.67
	AG5	5 905 183.55	273.10 ± 194.80	270.50 - 275.69
2009	**AG3**	4 380 263.39	262.41 ± 209.94	259.23 - 265.60
	AG4	7 541 007.87	258.13 ± 204.75	255.79 - 260.48
	AG5	6 999 601.92	261.63 ± 202.60	259.21 - 264.06
2010	**AG3**	4 107 105.99	283.03 ± 222.45	279.41 - 286.65
	AG4	7 314 826.33	272.30 ± 223.59	269.62 - 274.97
	AG5	7 172 952.67	277.89 ± 211.89	275.30 - 280.47
2011	**AG3**	2 941 583.22	336.14 ± 186.03	332.24 - 340.04
	AG4	4 727 121.57	323.86 ± 192.54	320.74 - 326.99
	AG5	4 623 493.43	308.50 ± 192.54	305.55 - 311.45

** AG3: > 18 ≤ 45 years, AG4: > 45 ≤ 65 years, AG5: > 65 years.

To summarise tables 4.29 and 4.30, it can be stated that AG1 showed the highest average cost per asthma prescription over the four year study period in all age groups. The average cost per prescription also declined with each age bracket, with AG5 having the lowest average cost per prescription over the study period in this section of the private healthcare sector of South Africa.

Tables 4.31 to 4.32 indicate the influence of age on the average cost of asthma medicine items for the study period. Table 4.31 indicates the average cost in children (AG1) and

adolescents (AG2) while Table 4.32 shows the difference in the average cost of asthma medicine items between adults (AG3, AG4 and AG5).

Table 4.31: Asthma medicine item cost in children and adolescents from 2008 - 2011

Year	Age group**	Total cost of asthma medicine items (R)	Average cost of asthma item per R_x (SD) (R)	CI 95% (R)
2008	**AG1**	864 073.46	187.59 ± 200.47	184.05 - 191.14
	AG2	1 806 567.82	174.46 ± 188.32	172.09 - 176.84
2009	**AG1**	1 447 297.39	221.29 ± 205.63	217.72 - 224.88
	AG2	2 231 598.28	218.07 ± 206.93	215.16 - 220.99
2010	**AG1**	1 169 581.41	225.01 ± 153.49	220.83 - 229.18
	AG2	2 104 373.34	233.95 ± 158.50	230.67 - 237.22
2011	**AG1**	622 552.21	248.62 ± 126.79	243.65 - 253.59
	AG2	1 263 699.31	233.15 ± 127.88	229.75 - 236.56

** AG1: 0 – 7 years, AG2: > 7 ≤ 18 years.

From table 4.31 it emerges that the average cost of medicine items increased from 2008 to 2011 among both children and adolescents. AG1 showed that in 2008, the average cost per asthma medicine item was R187.59 ± R200.47 and increased to R248.62 ± R126.79 per asthma medicine item in 2011. Adolescents in AG2 showed an average asthma medicine cost of R174.46 ± R188.32 in 2008, while the average cost of asthma medicine item increased to R233.15 ± R127.88 in 2011. This indicates that although AG2 had a higher total cost of medicine items among adolescents and children, the average cost of medicine items of AG1 was higher than the average cost of medicine items in AG2.

In table 4.32, the influence of age groups in adults is presented in order to determine which age group has the highest average asthma medicine cost.

Table 4.32: Asthma medicine items cost in adults from 2008 - 2001

Year	Age group**	Total cost of asthma medicine items (R)	Average cost of asthma medicine item per R_x (SD) (R)	CI 95% (R)
2008	**AG3**	3 928 440.79	174.89 ± 196.06	173.02 - 176.76
	AG4	6 312 973.89	173.30 ± 209.39	171.92 - 174.68
	AG5	5 905 183.55	185.01 ± 194.80	183.55 - 186.47
2009	**AG3**	4 380 263.39	204.37 ± 209.94	202.23 - 206.51
	AG4	7 541 007.87	196.84 ± 204.75	195.27 - 198.42
	AG5	6 999 601.92	206.48 ± 202.60	204.82 - 208.15
2010	**AG3**	4 107 105.99	217.36 ± 170.46	214.93 - 219.80
	AG4	7 314 826.33	207.72 ± 165.47	205.99 - 209.45
	AG5	7 172 952.67	218.28 ± 162.85	216.52 - 220.04
2011	**AG3**	2 941 583.22	235.57 ± 144.95	233.03 - 238.11
	AG4	4 727 121.57	226.31 ± 142.89	224.37 - 228.25
	AG5	4 623 493.43	230.07 ± 140.97	228.12 - 232.02

** AG3: > 18 ≤ 45 years, AG4: > 45 ≤ 65 years, AG5: > 65 years.

From table 4.32 it can be seen that the average cost per asthma medicine item increased throughout the study period for all three adult age groups. The same trends were also seen among children and adolescents. AG3 had the second highest average medicine cost per item between the three adults age groups ranging from R174.89 ± R196.06 in 2009 to R235.57 ± R144.95 in 2011. AG4 had an average cost of asthma medicine items ranging R173.30 ± R209.39 in 2008 and R226.31 ± R142.89 in 2011. AG5 had the highest average cost per medicine item for adults ranging from R185.01 ± R194.80 in 2008 to R230.07 ± R140.94 per in 2011.

To conclude the discussion on the average cost per asthma medicine item between age groups, the following can be noted: (1) that children in AG1 incurred the highest average cost per medicine item, (2) followed by AG5. These findings are, of course, in the context of the five age groups in this section of the private healthcare sector of South Africa.

4.5 PREVALENCE OF COPD IN ASTHMA

Asthma and COPD are the most common obstructive airway diseases in our community (Gibson & Simpson, 2009:728). The main difference between asthma and COPD patients are that COPD patients are mainly adults and in the economically productive age bracket, while asthma is more common among children (Campos & Lemos, 2009:306). From this perspective, the financial cost of COPD exceeds those of asthma (Campos & Lemos, 2009:306).

4.5.1 Combinations of asthma medications

Asthma and COPD cause a great deal of human suffering and significant financial loss, not only for the patients and their families but also the government. Therefore, these constitute serious public health problems around the world. This points to a great need for extending drug efficacy studies to include patients suffering from the overlapping of asthma and COPD, in this way addressing the many research opportunities for investigating the mechanism and treatment of overlapping asthma and COPD in patients (Gibson & Simpson, 2009:734).

The tables below indicate the top ten asthma medications (with their cost information) prescribed to patients with asthma alone, as well as those medications prescribed for patients with both asthma and COPD. A brief discussion of the top three medications with their pharmacology classification follows. The economic burden of COPD in asthma patients is then compared to the economic burden caused by asthma patients without COPD as co-morbidity.

4.5.2. Treatment cost of asthma and COPD

When asthma patients are classified according to severity and control (as indicated in section 2.2.3), a step wise approach is used in the treatment of these asthma patients (refer

to section 2.5). Asthma treatment is based on severity and usually commences with inhaled short acting β_2–agonist for mild asthma to inhaled corticosteroids with LABAs and SR theophylline for patients with severe persistent asthma. The pillar of asthma treatment is the use of ICSs and LABAs combinations (see Chapter 2, section 2.6). The treatment for COPD is based on the same principles as asthma treatments; its treatment guidelines are shown in appendix C. For the purpose of this study, only the ten most prevalent active ingredients are summarised in Table A1-A32 (refer to appendix A) while the most prevalent prescriptions are discussed. Tables 4.33 – 4.40 indicate the number of prescriptions with total cost of asthma and asthma-COPD medication items claimed through the database.

4.5.2.1 Single Products

Table 4.33 shows single medicine items per prescription for asthma and asthma-COPD patients for the years 2008 to 2011. The CPI was calculated between the percentage total cost and percentage prevalence (number of prescriptions) for asthma and asthma-COPD patients for the four year study period (refer to section 3.6.3.3).

Table 4.33: A summary of prescriptions containing a single asthma and/or COPD product claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	39 254	7 875 596.44	13 258	23 79 258.50
2009	56 647	12 015 163.80	18 177	4 728 818.05
2010	51 839	11 631 273.71	16 191	4 123 585.96
2011	29 979	7 861 019.41	12 601	2 954 579.61
Total values	177 719	39 383 053.36	60 227	14 186 242.12
CPI	0.98		1.04	

Table 4.33 shows that there were more single item prescriptions prescribed to patients with only asthma than single medicine items for patients with asthma and COPD. A total number of 177 719 prescription were issued to patients who had only asthma; these prescriptions cost R39 383 053.36, while prescriptions for those suffering from both asthma and COPD

comprised 60 227 prescriptions and amounted to R14 186 242.12. A single asthma-COPD item was more expensive than a single asthma item throughout the study period.

The most prevalent single medicine item prescribed over the four year study period was fluticasone for asthma patients and theophylline for patients who had asthma and COPD together.

4.5.2.1.1 Prescriptions containing a single asthma and/or COPD medicine items for 2008

From table A1-A4 the following observations can be made regarding single-item prescriptions:

The top three most frequently used single medications prescribed for patients with asthma in 2008 were:

- Fluticasone (n = 10 555, R312.29 ± R69.03) – an inhaled corticosteroid, salbutamol (n = 4 569, R37.33 ± R23.96) – a short–acting β_2 agonists and a combined product budesonide/formoterol that consists of an inhaled corticosteroid and a LABA (n = 4 331, R319.15 ± R79.89) was the most prevalent single asthma products.
- The top three single most frequently used medications prescribed to patients who experienced both asthma and COPD were theophylline (n = 4 214, R111.10 ± R52.09), fluticasone (n = 2 069, R336.38 ± R72.89) and a combination product fenoterol/ipratropium (n = 1 381, R181.93 ± R67.57).
- Theophylline is a controller medication but has a weak anti-inflammatory effect. Fluticasone is a controllers/anti-asthmatics and the combination product is a blend of a controller and reliever.
- In 2008 39 254 single items were prescribed for asthma patients. The total cost of asthma medication was R7 875 596.44. The most expensive asthma product was budesonide/formoterol with an average cost of R319.15 ± R79.86.
- For asthma patients who were also diagnosed with COPD, 13 258 single items were prescribed at a total cost of R23 79 258.50. Here the most expensive drug was also budesonide/formoterol (R336.38 ± R72.89).

4.5.2.1.2 Prescriptions containing a single asthma and/or COPD medicine items for 2009

From table A2 in appendix A it emerges that:

- The top three single medications were again fluticasone (n = 13 798, R351.48 ± R73.81), salbutamol (n = 9 094, R35.07 ± R23.50) and a combined product of budesonide/formoterol (n = 7 562, R355.12 ± R91.81).
- The top three asthma and COPD combination products were theophylline (n = 4 795, R114.77 ± R60.01), tiotropium (n = 3 156, R520.01 ± R278.21) and fluticasone (n = 2 457, 373.07 ± 80.50).
- In 2009, 56 647 single items were prescribed to asthma patients. The total cost of asthma medication claimed was R12 015 163.80.
- The most expensive asthma product was budesonide/formoterol with an average cost of R355.15 ± R91.81.
- For asthma patients who were also diagnosed with COPD, there were 4 728 818.05 single items prescribed with a total cost of R23 79 258.50 claimed though the database. The most expensive drug was tiotropium with an average cost of R520.01 ± R278.21.

4.5.2.1.3 Prescriptions containing a single asthma and/or COPD medicine items for 2010

Table A3 shows the same trend as 2008 and 2009 with

- The top three medications being fluticasone (n = 11 458, R371.68 ± R81.60) (n = 7 745, R34.59 ± R20.22 and a combinations product budesonide/formoterol that (n = 7 612, R372.36 ± R102.23).
- The top three single medications for asthma and COPD were theophylline (n = 4 542, R122.53 ± R61.36) fluticasone (n = 2 186, R389.85 ± R99.93) and tiotropium (n = 2 034, R528.51 ± R122.32).
- In 2010, 51 839 single items were prescribed for asthma patients. The total cost of asthma medication claimed was R11 631 273.71.
- The most expensive drug for asthma patients was again budesonide/formoterol with an average cost now reaching R372.36 ± R102.23.For those asthma patients also diagnosed with COPD, 16 191 single items were prescribed, with a total cost of R4 123 585.96 claimed though the database.

- Tiotropium was also the most expensive drug per prescription for 2010 with R528.51 ± R122.32.

4.5.2.1.4 Prescriptions containing a single asthma and/or COPD medicine items for 2011

From table A4 it emerges that

- The top three medications were budesonide/formoterol that consist of an inhaled corticosteroid and a long–acting β_2-agonists (n = 5 707, R378.61 ± R94.50) and another combination product salmeterol/fluticasone (n = 5 314, R289.17± R50.20) that also consists of an inhaled corticosteroid and a long–acting β_2 agonists and fluticasone (n = 3910, R347.95 ± R104.06).
- Fluticasone, budesonide/formoterol and salmeterol/fluticasone are both controllers/anti-asthmatics. This suggests that asthma patients 2011 had more severe asthma because they used ICS combinations.
- The top three asthma and COPD combination products were theophylline (n = 4 106, R116.92 ± R60.18) a combination product of salmeterol/fluticasone (n = 1 754, R307.00 ± R52.50) and another combinations product budesonide/formoterol (n = 1 490, 395.37 ± 109.12).
- In 2011, 29 979 single items were prescribed to asthma patients. The total cost of asthma medication claimed was R7 861 019 of which budesonide/formoterol had the highest cost per prescription for 2011 with R378.61 ± R94.50.
- For asthma patients also diagnosed with COPD, a total number of 12 601 single items were prescribed, with tiotropium again being the most expensive prescribed drug for 2011 (R534.85 ± R142.76).
- Fluticasone-containing products were the most regularly prescribed item with a total number of 39 721 prescriptions over the four years for asthma patients. A total number of 17 657 prescriptions of theophylline were claimed for patients who had asthma together with COPD.
- Budesonide/formoterol was the most expensive single drug prescribed for asthma over the study period and for asthma and COPD together, it was tiotropium. Tiotropium was also more expensive (R156.24 ± R48.26) than budesonide/formoterol.

4.5.2.2 Two Products

The following table provides information on combination of different products prescribed together to asthmatic patient during the study period. The number of prescriptions becomes smaller as the number of products on the prescription increases**.** The number of asthmatic and or COPD items on the prescription ranges between two and eight medicine items. Dispensing of such prescriptions indicates that the patient has a mild to severe asthma condition. Thus, one expects that more controller medications and glucocorticoids will be prescribed (refer to section 2.7).

The two item prescriptions for asthma as well as asthma with COPD are summarised in table A5-A8 (refer to appendix A). The CPI was calculated between the percentage total cost and percentage prevalence (number of prescriptions) for asthma and asthma-COPD patients for the four year study period (refer to section 3.6.3.3).

Table 4.34: A summary of prescriptions containing two asthma and/or COPD products claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	19 085	6 376 646.96	4 361	1 516 839.81
2009	18 380	7 288 521.77	7 202	3 857 074.76
2010	16 654	6 984 882.18	6 466	3 382 048.39
2011	11 095	4 559 337.45	4 106	1 800 425.24
Total values	65 214	25 209 388.36	22 135	10 556 415.20
CPI	0.94		1.16	

Table 4.34 indicates that prescriptions containing two medicine items for asthma and asthma with COPD were far less prevalent than single item prescriptions for asthma and asthma with COPD. There were 65 214 prescriptions with a total cost of R25 209 388.36 prescribed for patients with asthma, while patients with asthma and COPD received 22 135 prescriptions with a total cost of R10 556 415.20. Two item asthma-COPD prescriptions were more expensive than two item asthma prescriptions for the study period.

4.5.2.2.1 Prescriptions containing two asthma and/or COPD medicine items for 2008

The following findings can be made regarding the year 2008:

- There were 19 085 two-item prescriptions prescribed for asthma patients, with 477 different combinations of items.
- The top three prescriptions prescribed for asthma patients were fluticasone and salbutamol (n = 1 490; R356.56 ± R78.11) salbutamol and budesonide (n = 1364; R232.24 ± R53.04) and fluticasone and montelukast (n = 1 017; R617.19 ± R111.92).
- Fluticasone and salbutamol were the two active ingredients that were most prevalent in the medicine items prescribed for asthma patients.
- For asthma-COPD patients there were 4 361 two-item prescriptions with 111 different combinations.
- The most expensive drug prescribed for asthma patients was fluticasone and montelukast with an average cost per prescription of R617.19 ± R111.92.
- The three most prevalent combinations prescribe for asthma with COPD were fenoterol/ipratropium and theophylline (n = 490; R305.25 ± R110.81), fluticasone and theophylline (n = 397; R484.09 ± R83.80) and theophylline and salbutamol (n = 343; R145.75 ± R73.80).
- Theophylline was the most prevalent drug, appearing eight times in the top ten two-item prescriptions for asthma and COPD patients.
- The prescription of fenoterol/ipratropium and fluticasone had the highest average cost for two products medicine on an asthma-COPD prescription in 2008 with R541.26 ± R105.15.

4.5.2.2.2 Prescriptions containing two asthma and/or COPD medicine items for 2009

The following findings can be made regarding the year 2009:

- There was an increase in two item prescriptions for both asthma (N = 18 380) and asthma/COPD (N = 7 202).
- There were 374 different combinations for asthma prescriptions. The top three asthma combinations were fluticasone and montelukast (n = 1 900; R697.57± 153.53),

fluticasone and salbutamol (n = 1674; R402.13 ± 75.19) and salbutamol and fluticasone (n = 820; R389.79 ± 72.59).

- The most expensive drugs for asthma prescriptions were montelukast and budesonide/formoterol with an average cost of R716.35 ± R152.77 in 2009
- There were 120 different two-item prescription combinations for asthma/COPD patients of which the following were the most prevalent: fluticasone and tiotropium (n = 813; R880.63 ± R126.42), fenoterol/ipratropium and theophylline (n = 463; R321.67 ± R105.94), and tiotropium and budesonide/formoterol (n = 431; R889.23 ± R159.93).
- The avarge cost of tiotropuim and budesonide/formoterol was R880.63 ± R126.42 in the two-item prescriptions for asthma and COPD, which higher than the most expensive two-item prescription of asthma patients (R716.35 ± R716.35 ± 152.77).

4.5.2.2.3 Prescriptions containing two asthma and/or COPD medicine items for 2010

The following findings can be made regarding the year 2010:

- 2010 saw a decrease in total prescriptions from 2009 with 16 646 asthma prescriptions and only 6 466 asthma/COPD observations.
- There were 374 different combinations of two-item asthma prescriptions and only 129 different combinations for asthma/COPD prescriptions.
- The most expensive drugs for asthma prescriptions were montelukast and budesonide/formoterol with an average cost of R729.63 ± R140.06 in 2010
- Fluticasone and montelukast were the most prevalent asthma prescription with 1687 two item prescription with an average cost of R729.63 ± 140.06 followed by 1369 prescriptions of fluticasone, salbutamol (R416.45 ± 88.75) and 813 prescriptions of montelukast, budesonide/formoterol (R754.05 ± 151.61).
- Fluticasone and tiotropium were the most prevalent asthma/COPD combination with 543 prescriptions and an average cost of R906.50 ± R129.51 followed by fenoterol/ipratropium, theophylline with 461 prescription and average cost of R327.57 ± R95.82.and fluticasone and theophylline with 410 prescriptions (R548.99 ± R109.54).
- Tiotropium and budesonide/formoterol were the most expensive drugs for asthma and COPD patients with an average cost of R913.74 ± R197.34 in 2010

4.5.2.2.4 Prescriptions containing two asthma and/or COPD medicine items for 2011

The following findings can be made regarding the year 2011:

- In 2011, 192 different combinations were found for asthma prescriptions and only 94 combinations for asthma-COPD.
- Asthma patients received 11 095 prescriptions, of which salbutamol and budesonide (n = 793; R266.41± 60.47), budesonide and formoterol (n = 662; R286.05 ± 135.94) and budesonide and salbutamol (n = 575; R277.40 ± 51.30) were most prevalent.
- Budesonide was the most prevalent drug in the top three asthma patients.
- Montelukast and budesonide/formoterol were the most expensive asthma prescriptions (R788.60 ± R134.92).
- Asthma-COPD prescriptions numbered 4 106, of which the top three were mostly combination products with theophylline: 490 prescriptions of Salmeterol/fluticasone and theophylline with an average cost of R428.44 ± R64.40, 419 prescriptions with fenoterol/ipratropium and theophylline with an average cost of R318.01 ± R85.05, and 238 prescriptions with theophylline and budesonide/formoterol (R450.19 ± R106.50).
- Another combination of budesonide/formoterol and theophylline had the highest average cost for asthma-COPD patients R556.20 ± R142.83 in 2011 and was the most expensive prescription for 2011 for asthma and asthma-COPD patients.

4.5.2.3 Three Products

The three-item prescriptions for both asthma and asthma and COPD are summarised in table A9-12 (refer to appendix A). The CPI was calculated between the percentage total cost and percentage prevalence (number of prescriptions) for asthma and asthma-COPD patients for the four year study period (refer to section 3.6.3.3).

Table 4.35: A summary of prescriptions containing three asthma and/or COPD product claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	5 955	2 889 888.46	1 403	742 350.29
2009	4 218	2 441 832.29	2 813	2 221 171.25
2010	3 921	2.376 538.57	2 533	1 970 006.74
2011	2 567	1 455 213.23	1 115	736 716.41
Total values	16 661	9 163 472.55	7 864	5 670 244.69
CPI	0.91		1.19	

Table 4.35 indicates prescriptions with three items and cost with asthma and asthma-COPD combinations. The frequency was noticeably lower than the single and two-item prescriptions of which 16 661 were asthma prescriptions amounting to R9 163 472.55. Asthma-COPD patients were issued 7 864 prescriptions with the total cost of R5 670 244.69. Asthma-COPD three item prescriptions were more expensive when compared to the CPI of three items per prescription for asthma patients throughout the study period.

4.5.2.3.1 Prescriptions containing three asthma and/or COPD medicine items for 2008

The following findings can be made regarding the year 2008:

- Asthma patients received 1 021 combinations of prescriptions and 5 955 in 2008.

- Asthma patients with COPD received only 1 403 prescriptions and 171 combinations of drugs on three-item prescriptions.
- The combination of fluticasone, montelukast and salbutamol was the most prevalent asthma combination in 2008 with 325 prescriptions and an average cost of R674.83 ± R102.16.
- Asthma patients with COPD received 99 prescriptions of the combination fenoterol/ipratropium, fluticasone and theophylline with an average cost of R635.47 ± R145.35. This was also the highest average cost for patients with combination of asthma with COPD
- The most expensive combination for asthma product was fenoterol/ipratropium, fluticasone and theophylline with an average cost of R680.70 ± R59.48 per prescription.

4.5.2.3.2 Prescriptions containing three asthma and/or COPD medicine items for 2009

The following findings can be made regarding the year 2009:

- For asthma patients, the number of three item prescriptions decreased to 4 128 from 2008, while asthma and COPD items per prescription increased to 2 813.
- The same trends are prevalent in 2009 as the combination of fluticasone, Montelukast, salbutamol was again most prevalent for asthma patient with 358 observations an increased average cost of R747.53 ± R112.25 per prescription.
- Asthma/COPD patients were issued with a new top prevalent prescription, namely a combination of fluticasone, tiotropium, and theophylline, which was observed 231 times. The average cost also increased considerably to R1 074.20 ± R215.32 per prescription. This was also the most expensive combination of three products for asthma with COPD in 2009.
- Fenoterol/ipratropium, fluticasone and montelukast were the most expensive prescriptions for asthma patients with an average cost of R942.13 ± R190.99 per prescription

4.5.2.3.3 Prescriptions containing three asthma and/or COPD medicine items for 2010

The following findings can be made regarding the year 2010:

- The number of three item prescriptions prescribed for both asthma and asthma/COPD patients declined during 2010.
- 314 of the 3 921 prescriptions were for fluticasone, montelukast, salbutamol were the same in 2008 and 2009, but the average cost increased to R778.50 ± R131.96 for asthma prescriptions.
- 220 of the 2 533 prescriptions included fluticasone, Tiotropium, and theophylline; however this combination was more expensive than the asthma combination with an average cost of R1118.57 ± R163.03 for an asthma with COPD prescription.
- With 72 observations, the combination of montelukast, budesonide/formoterol and theophylline was the most expensive drug for asthma prescription containing three drugs (R942.66 ± R107.22).

4.5.2.3.4 Prescriptions containing three asthma and/or COPD medicine items for 2011

The following findings can be made regarding the year 2011:

- 2011 had again the lowest number of prescriptions for both asthma (N = 2 567) and asthma/COPD (N = 1 115).
- Salbutamol, budesonide and formoterol had 112 observations with an average cost of R342.52 ± R160.64 per prescription for asthma patients.
- Fenoterol/ipratropium, salmeterol/fluticasone, theophylline had 104 observations with an average cost of R656.55 ± R98.71 per prescription. This is almost twice as many as the second most prevalent asthma/COPD prescription with three items.
- The combination of fluticasone, tiotropium and theophylline was the most expensive drug for asthma/COPD prescriptions (R1067.27 ± R198.74 per prescription).

Asthma prescriptions with salmeterol/fluticasone, montelukast and salbutamol (R690.87 ± R125.66) had the highest average cost per prescription but still showed a lower average than the asthma/COPD combination

4.5.2.4 Four Products

The four-item prescriptions for both asthma and asthma and COPD are summarised in table A14-17 (refer to appendix A). The CPI was calculated between the percentage total cost and percentage prevalence (number of prescriptions) for asthma and asthma-COPD patients for the four year study period (refer to section 3.6.3.3).

Table 4.36: A summary of prescriptions containing four asthma and/or COPD product claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	1 271	796 764.67	177	134 688.52
2009	884	687 687.25	809	877 062.29
2010	776	634 102.05	596	675 083.15
2011	335	266 222.49	116	143 208.16
Total values	3.266	2 384 801.21	1 698	1 830.042.12
CPI	0.86		1.27	

Table 4.36 shows prescriptions with four items. These prescriptions are associated with severe asthma patients. For asthma patients, the total number of prescriptions came to 3 266 prescriptions with a total cost of R2 384 801.21. Asthma with COPD patients received 1 698 prescriptions with a total cost of R1 830 042.12 from 2008 to 2011. The frequency declined again for both asthma and asthma-COPD patients. The CPI calculated for four item prescriptions for asthma-COPD was 1.27 and for asthma four item prescriptions was 0.86. This indicated that the four item prescriptions for asthma-COPD was more expensive when compared to four item prescriptions for asthma throughout the study period.

4.5.2.4.1 Prescriptions containing four asthma and/or COPD medicine items for 2008

The following findings can be made regarding the year 2008:

- Asthma (N = 1271; 580 combinations) had a greater prevalence than asthma/COPD (N = 177; 59 combinations) for four-item prescriptions.
- 23 prescriptions with an average cost of R891.64 ± R65.30 per prescription contained the combination of fluticasone, montelukast, theophylline and salbutamol. This was also the most expensive four-item prescription combination for asthma patients
- 9.6% of the asthma/COPD patients had to pay an average of R940.20 ± 121.05 per prescription for the combination of salbutamol/ipratropium, fenoterol/ipratropium, theophylline, fluticasone.
- However, the above combination for asthma with COPD patients was not the most expensive prescription. The highest average cost of R991.91 ± R147.70 per prescription and with only 10 observations was ipratropium/salbutamol, budesonide/formoterol, theophylline and salbutamol.

4.5.2.4.2 Prescriptions containing four asthma and/or COPD medicine items for 2009

The following findings can be made regarding the year 2009:

- Asthma and asthma/COPD four-item prescription prevalences are in close proximity with each other.
- Asthma patients received 884 prescriptions with 360 combinations while asthma/COPD were issued with 809 prescriptions with just 147 combinations.
- 3.50% (n = 31; N = 884) of theophylline, montelukast, budesonide/formoterol, salbutamol were the most prevalent in asthma prescriptions with four items.
- 8.12% (n = 66; N = 809) of theophylline, fluticasone, tiotropium, salbutamol was prescribed for asthma with COPD patients in the four-item prescriptions.
- The average cost for the asthma combination was R786.95 ± R65.95 per prescription while the average cost for the asthma/COPD prescription was R1 067.11 ± R177.80.
- Fenoterol/ipratropium, fluticasone, budesonide/formoterol and theophylline combination were the most expensive asthma prescription with an average cost of R1 203.76 ± R87.93 per prescription.

- Fenoterol/ipratropium, fluticasone, tiotropium and theophylline had the highest average cost for asthma with COPD prescriptions (R1 250.75 ± R79.14 per prescription).

4.5.2.4.3 Prescriptions containing four asthma and/or COPD medicine items for 2010

The following findings can be made regarding the year 2010:

- The prevalence of both asthma (N = 776) and asthma and COPD (n = 596) dropped in this year.
- 36 four-item asthma prescriptions contained the following combination: fluticasone, montelukast, theophylline and salbutamol. The average cost for this prescription was R1 027.94 ± R95.70.
- Fenoterol/ipratropium, fluticasone, tiotropium, theophylline had 48 observations and an average cost of R1 317.65 ± R154.17 per prescription for patients who had asthma/COPD. This was also the most expensive asthma/COPD prescription.
- There were 334 different combinations for asthma four-item prescriptions of which fenoterol, fluticasone, montelukast and theophylline combination had the highest average cost of R1 178.41 ± R32.83 per prescription.

4.5.2.4.4 Prescriptions containing four asthma and/or COPD medicine items for 2011

The following findings can be made regarding the year 2011:

- 2011 had the lowest total number of fouritem prescriptions in the four year study period.
- Asthma patients received 335 four-item prescriptions with 98 combinations.
- COPD/asthma prescriptions showed only 34 combinations and 116 four-item prescriptions were issued in 2011.
- The most prevalent combinations for asthma patient were ciclesonide, prednisone, salmeterol and salbutamol with 19 prescriptions for 2011 and an average cost of R777.66 ± R128.97 per prescription.
- 15 prescriptions were issued for tiotropium, budesonide/formoterol, theophylline, salbutamol at an average cost of R1 170.09 ± R49.44 per prescription.
- 14 prescriptions for fenoterol/ipratropium, fluticasone, tiotropium, theophylline at a slightly higher average cost than the prescription above, namely of R1 473.77 ± R125.29 per asthma/COPD were issued.

- The most expensive prescription for asthma with COPD patients were salbutamol/ipratropium, fluticasone, tiotropium and theophylline with an average cost of R1 684.12 ± R81.51 per prescription.
- Asthma prescriptions with fenoterol, budesonide, budesonide/formoterol and theophylline had the highest average cost of R1 032.69 ± R00.00.

4.5.2.5 Five Products

The five-item prescriptions for both asthma and asthma and COPD are summarised in Table A18-21 (refer to appendix A). The CPI was calculated between the percentage total cost and percentage prevalence (number of prescriptions) for asthma and asthma-COPD patients for the four year study period (refer to section 3.6.3.3).

Table 4.37: A summary of prescriptions containing five asthma and/or COPD product claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	248	198 501.39	21	19 746.40
2009	141	144 995.12	107	152 115.14
2010	157	158 761.13	71	99 231.36
2011	32	29 305.90	18	29 081.66
Total values	578	531 563.54	217	300 174.56
CPI	0.87		1.21	

Table 4.37 shows five items on a prescription for asthma and asthma-COPD patients. The frequency decreased rapidly if compared to the previous prescriptions with fewer items. There were only 578 asthma prescriptions with five items with a total cost of R531 563.54. Asthma and COPD showed the same trend as asthma patients with a decrease in frequency as the number of items on a prescription increased. There were 217 prescriptions consisting of five items and a cost of R300 174.56 for asthma and COPD patients throughout the study period. It can therefore be concluded that five item prescriptions for asthma-COPD is more expensive when compared to five item prescriptions for asthma throughout the study period**.**

4.5.2.5.1 Prescriptions containing five asthma and/or COPD medicine items for 2008

The following findings can be made regarding the year 2008:

- There were 248 five-item prescriptions for asthma patients with a total of 164 different combinations, while asthma and COPD were issued with only 21 five item prescriptions for the year 2008, featuring nine different combinations.
- 12 of the 248 asthma prescriptions consisted of beclomethasone, fenoterol, budesonide, theophylline, budesonide/formoterol and average cost of R807.51 ± R29.08.
- The most prevalent asthma with COPD prescription had a prevalence of a six observations with five different combinations for five-item prescriptions.
- Salbutamol, fenoterol/ipratropium, theophylline, fluticasone, salbutamol combination were the most prevalent five-items asthma prescription with an average cost of R845.94 ± R0.77 per prescription; there were six observations in 2008 for asthma patients.
- The combination of bromhexine/orciprenaline, fenoterol/ipratropium, salbutamol/ipratropium, formoterol, theophylline and fluticasone was the most expensive prescription for asthma with COPD patients with five observations; the average cost was R1 070.04 ± R99.25 per prescription.
- The asthma prescriptions that contain the following products prednisone, fluticasone, theophylline and salbutamol had the highest average cost of R1 257.32 ± R00.00 per prescription for 2008.

4.5.2.5.2 Prescriptions containing five asthma and/or COPD medicine items for 2009

The following findings can be made regarding the year 2009:

- In 2009, asthma patients received 141 prescriptions with five items with 84 combinations of drugs, while asthma/COPD prescriptions with five items increased from 21 observations in 2008 to 107, with 47 different combinations in 2009.
- The five-item asthma prescription that were most prevalent was theophylline, fluticasone, salmeterol, montelukast, salbutamol with a prevalence of 12 and an average cost of R1098.37 ± R181.40 per prescription.

- Theophylline, prednisone, fluticasone, tiotropium, salbutamol appeared 12 times in 2009 with an average cost of R1080.35 ± R1130.64 per prescription.
- Asthma with COPD patients also received two five-item prescriptions appearing 11 times; the first is the combination of fenoterol/ipratropium, formoterol, fluticasone, tiotropium, theophylline with an average cost of R1703.93 ± R519.88 per prescription, and
- The other asthma/COPD prescription contained ipratropium/salbutamol, tiotropium, budesonide/formoterol, theophylline, salbutamol and had an average cost of R1262.93 ± R86.50 per prescription.
- Asthma prescriptions with ipratropium/salbutamol, theophylline, prednisone, fluticasone and salbutamol had the highest average cost of R1306.80 ± R64.39 per prescription.

4.5.2.5.3 Prescriptions containing five asthma and/or COPD medicine items for 2010

The following findings can be made regarding the year 2010:

- The same trends in terms of prevalence continued in 2010 as were seen in 2008 and 2009. There were more asthma prescriptions (157 with 92 combinations) than asthma/COPD ones (71 with 31 combinations).
- 11 out of the 157 asthma prescriptions were for the ipratropium, fluticasone, montelukast, theophylline, and salbutamol combination with an average cost of R1 194.47 ± R50.96 per prescription.
- 10 out of the 71 asthma/COPD prescriptions had the combination of fenoterol/ipratropium, fenoterol/ipratropium, fluticasone, tiotropium and theophylline with an average cost of R1 676.07 ± R63.69 per prescription.
- The combination of ipratropium/salbutamol, theophylline, fenoterol, fluticasone and tiotropium was also the most expensive prescription for asthma/COPD patients R1 913.2 ± R00.00 per prescription. However, this combination only had two observations for the whole of 2010.
- With a total of five, the prescription for asthma patients that had salbutamol, salmeterol, montelukast, budesonide/formoterol and theophylline was the most expensive prescription to require (R1 416.01 ± R38.49) for asthma patients in 2010.

4.5.2.5.4 Prescriptions containing five asthma and/or COPD medicine items for 2011

The following findings can be made regarding the year 2011:

- 2011 had a very low prevalence of both asthma and asthma/COPD five-item prescriptions.
- Asthma had a prevalence of 32 observations with 14 different combinations of asthma medicine.
- Asthma/COPD had a prevalence of just 18 observations with nine different combinations.
- Six out of the 32 asthma prescriptions contained prednisone, beclomethasone, formoterol, theophylline and salbutamol with an average cost of R408.80 ± R00.00 per prescription; there were also six combinations of salmeterol /fluticasone, ipratropium, montelukast theophylline, salbutamol with an average cost of R1 009.15 ± R14.61 per prescription.
- 33.34% (N = 18; n = 6) of the five-items prescriptions for asthma with COPD patients had the combination of fenoterol/ipratropium, fenoterol/ipratropium, theophylline, fluticasone with an average cost of R1 686.23 ± R00.00 per prescription.
- There was only one observation for the year 2011 the asthma/COPD prescription containing salbutamol/ipratropium, fluticasone, Salmeterol, tiotropium and theophylline with an average cost of R1 801.69 ± R00.00 per prescription, which made it the most expensive prescription for the year 2010 of all the asthma-COPD prescriptions.
- The highest average cost for an asthma prescription was R1 546.42 ± R00.00 and contained only one observation of fenoterol/ipratropium, tiotropium, montelukast, budesonide/formoterol and theophylline in 2010

4.5.2.6 Six Products

The six-item prescriptions for both asthma and asthma and COPD are summarised in Table A22-24 (refer to appendix A). The CPI was calculated between the percentage total cost and percentage prevalence (number of prescriptions) for asthma and asthma-COPD patients for the four year study period (refer to section 3.6.3.3).

Table 4.38: A summary of prescriptions containing six asthma and/or COPD product claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	56	62 170.49	14	15 998.64
2009	14	15 998.64	10	14 439.00
2010	61	81 466.40	3	3 909.15
2011	3	5 498.82	7	15 025.88
Total values	134	165 134.35	34	49 372.44
CPI	0.97		1.14	

Table 4.38 indicates 134 prescriptions with six items for asthma patients and 34 prescriptions for asthma and COPD patients. The total cost for asthma patients were R165 134.35 and R49 372.44 for patients with asthma and COPD. Prescriptions containing six items for asthma-COPD patients were more expensive than asthma patient six item prescriptions throughout the study period.

4.5.2.6.1 Prescriptions containing six asthma and/or COPD medicine items for 2008

The following findings can be made regarding the year 2008:

- There were more six-item asthma prescriptions n = 56 than six-item asthma/COPD prescriptions n = 14 in 2008.

- 13 of the 56 asthma prescriptions consisted of zafirlukast, fenoterol, fluticasone, ipratropium, fluticasone and theophylline. The average costs for the 13 prescriptions were R1 463.73 ± R33.84 for asthma patients.
- For asthma/COPD patients there were two prescriptions of 14 consisting of Fenoterol /ipratropium, ipratropium, theophylline, fluticasone, montelukast and budesonide/formoterol. The average cost was R2 018.22 ± R72.85 per prescription. This prescription had the highest average cost in asthma of COPD prescriptions, was but also higher than asthma prescription costs for the same year.
- Asthma prescriptions containing betamethasone, salbutamol/ipratropium fenoterol/ipratropium, budesonide, budesonide/formoterol and theophylline were the most expensive with an average cost of R1 811.54 ± R00.00 per prescription.

4.5.2.6.2 Prescriptions containing six asthma and/or COPD medicine items for 2009

The following findings can be made regarding the year 2009:

- The frequency drastically dropped for asthma patients in 2009 if compared to 2008's six-item prescription prevalence.
- There were 14 six-item prescriptions for asthma patients; two of these consisted of fenoterol/ipratropium, ipratropium, theophylline, fluticasone, montelukast, and budesonide/formoterol. This prescription average cost was the highest for both asthma and asthma/COPD patients reaching R2 018.23 ± 72.58.
- The combination of bromhexine/orciprenaline, salbutamol/ipratropium, fenoterol/ipratropium, theophylline, fluticasone, tiotropium (R1 498.36 ± R52.42) consisted of 50% (n = 5; N = 10) of six-item prescriptions for 2009 in asthma patients with COPD.
- There six-item prescriptions with the combination of salbutamol, ipratropium/salbutamol, salbutamol/ipratropium, theophylline, tiotropium and budesonide/formoterol had the highest average cost of R1 522.43 ± R00.00 per prescription for asthma/COPD patients.

4.5.2.6.3 Prescriptions containing six asthma and/or COPD medicine items for 2010

The following findings can be made regarding the year 2010:

- Frequency increased from 2009 to 2010 with 61 observations of the six-item prescriptions for asthma patients.
- Asthma/COPD prescriptions were limited to only three different six-item combinations and the average cost per prescription ranged from R1 108.84 ± R00.00 for fenoterol/ipratropium, formoterol, theophylline, fenoterol/ipratropium, formoterol and theophylline to R1 407.16 ± R00.00 for tiotropium, budesonide/formoterol, theophylline, salbutamol, tiotropium and salbutamol.
- Eight of the 61 six-item asthma prescriptions had the following combination: salbutamol, ipratropium/salbutamol, methyl prednisone, montelukast, tiotropium, and theophylline. This was the most prevalent six-item prescription for asthma patients. The average cost was R1 332.30 ± R 00.00 per prescription.
- There were also six asthma prescriptions containing theophylline, prednisone, montelukast, tiotropium, budesonide/formoterol, salbutamol. The average cost was slightly higher than the previous combinations (R1 415.98 ± R39.08 per prescription).
- The average cost of R1 577.63 ± R46.84 per prescription for an asthma prescription containing formoterol, prednisone, theophylline, montelukast, budesonide/formoterol and salbutamol was the most expensive prescription for asthma patients.

4.5.2.6.4 Prescriptions containing six asthma and/or COPD medicine items for 2011

The following findings can be made regarding the year 2011:

- This was the only year that had more asthma/COPD (N = 7) prescriptions than asthma (N = 3) prescriptions over the four year study period.
- The combination with the highest average cost per asthma prescription was salbutamol, fenoterol/ipratropium, tiotropium, montelukast, budesonide/formoterol and theophylline with an average cost of R2 469.26 ± R00.00 per prescription.
- For asthma patients, the combination of salbutamol, fenoterol/ipratropium, tiotropium, montelukast, budesonide/formoterol, theophylline with three two was most prevalent with an average cost of R1 514.73 ± R00.00 per prescription.

- The asthma/COPD prescription with the most observations (n = 3) was fenoterol/ipratropium, fenoterol/ipratropium, fluticasone, salmeterol, tiotropium and theophylline. The average cost of such a prescription was R2 196.06 ± R63.98 per prescription. However,
- The most expensive prescription for asthma with COPD patients was fenoterol/ ipratropium, theophylline, fluticasone, tiotropium, fenoterol/ipratropium and salmeterol/fluticasone with an average cost of R2 708.74 ± R00.00 per prescription.

4.5.2.7 Seven Products

The seven-item prescriptions for both asthma and asthma and COPD are summarised in Table A25-28 (refer to appendix A). The CPI was not calculated because there were too few observations.

Table 4.39: A summary of prescriptions containing seven asthma and/or COPD product claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	11	14 609.34	1	618.20
2009	3	4 295.80	1	1 876.84
2010	2	1 815.70	1	2 759.63
2011	1	1 852	0	0

There were only 17 seven-item prescriptions for asthma patients and only three for asthma and COPD patients for the whole study period. The cost associated with seven-item prescriptions for asthma patients was R22 573.88 and R5 254.67 for asthma and COPD patients.

4.5.2.7.1 Prescriptions containing seven asthma and/or COPD medicine items for 2008

The following findings can be made regarding the year 2008:

- There were 11 prescriptions for asthma patients and only one for an asthma and COPD patient.

- There were three prescriptions consisting of ipratropium, fenoterol, fluticasone, prednisone isone, budesonide, montelukast and salbutamol. These had a total of R3 205.38 and an average cost of R 1068.46 ± R00.00 per prescription for asthma patients.
- Theophylline was the most prevalent drug appearing nine times on different prescriptions.
- The most expensive asthma prescription (R2 688.12 ± 00.00 per prescription) consisted of montelukast, tiotropium, theophylline, fluticasone, montelukast, tiotropium and theophylline.
- There was only one seven-item prescription for asthma and COPD patients that consisted of salbutamol, fenoterol/ipratropium, formoterol, salbutamol, fenoterol/ipratropium, formoterol and theophylline and had an average cost of R618.20 ± R00.00 per prescription.

4.5.2.7.2 Prescriptions containing seven asthma and/or COPD medicine items for 2009

The following findings can be made regarding the year 2009:

- There were only four prescriptions prescribed for asthma and again only one for asthma and COPD patients.
- Asthma/COPD had one prescription with fluticasone, tiotropium, theophylline, salbutamol, fenoterol/ipratropium, fluticasone and theophylline.
- The average cost for this prescription was R1 876.84 ± 00.00. There was one asthma prescription that had the exact same combination as the above mentioned
- The average cost per seven-item asthma prescription ranged from R1 161.69 ± R00.00 per prescription (Ipratropium, bromhexine/orciprenaline, ipratropium/salbutamol, prednisone theophylline, and montelukast**)** to R1 876.84 ± R00.00 per prescription (fluticasone, tiotropium, theophylline, salbutamol, fenoterol/ipratropium, fluticasone and theophylline) for asthma patients

4.5.2.7.3 Prescriptions containing seven asthma and/or COPD medicine items for 2010

The following findings can be made regarding the year 2010:

- There were only two asthma prescriptions and one for asthma/COPD for the whole of 2010.
- Asthma/COPD had the highest average cost of the three prescriptions (R2 759.63 03 ± R00.00 per prescription). It consisted of fenoterol/ipratropium, theophylline, fluticasone, tiotropium, fenoterol/ipratropium, salmeterol/fluticasone and theophylline
- The average costs per asthma prescription ranged from R787.03 ± R00.00 per prescription for bromhexine/orciprenaline, betamethasone theophylline, prednisone budesonide/formoterol, salbutamol and salbutamol to R1 028.67 03 ± R00.00 per prescription for a prescription containing prednisone, ipratropium, ipratropium, prednisone theophylline, fluticasone and salbutamol.
- The asthma patients had two prednisone products on the one prescription and two salbutamol products on the other prescription.

4.5.2.7.4 Prescriptions containing seven asthma and/or COPD medicine items for 2011

The following findings can be made regarding the year 2011:

- There was one seven-item prescription for an asthma patient that consisted of salbutamol, budesonide, fenoterol/ipratropium, tiotropium, montelukast, budesonide, formoterol and theophylline with an average cost of R1 852.54 ± 00.00.
- There was no seven-item prescription for asthma/COPD patients.

4.5.2.8 Eight Products

The eight-item prescriptions for both asthma and asthma-COPD are summarised in Table A29-32 (refer to appendix A). The CPI was not calculated because there where to few observations.

Table 4.40: A summary of prescriptions containing eight asthma and/or COPD product claimed

Year	Asthma		Asthma and COPD	
	Number of prescriptions	Total cost (R)	Number of prescriptions	Total cost (R)
2008	1	2 064.61	1	1 274.17
2009	1	1 274.71	1	1 274.17
2010	1	1 274.74	0	0
2011	1	1.274.74	0	0

Prescriptions with eight items had the lowest prevalence for both asthma and asthma-COPD patients. A total number of six prescriptions with eight asthma items were issued; four were for asthma patients and two for patients with asthma and COPD. The total costs for asthma prescriptions with eight items were R5 956.03 from 2008 to 2011 and R2 548.94 for asthma and COPD for 2008 and 2009. These were summarised in table 4.40. No eight–item combination prescription was issued for asthma and COPD patients in 2010 and in 2011. Because there were only six prescriptions with eight items during the entire study period, the present discussion involves data from all four years. These findings can be made for 2008 to 2011:

- In 2009, 2010 and 2011 asthma patients were issued with the same items on their prescriptions that include the following: fenoterol/ipratropium, budesonide/formoterol, salbutamol, fenoterol/ipratropium, prednisone, budesonide/formoterol, montelukast and salbutamol. The average cost for this prescription was the same (R1 274.17 ± R00.00 per prescription) for all three years.
- In 2008 the prescriptions were different from the other three years in that only two items stayed the same. These were fenoterol/ipratropium and montelukast. The prescription was made up from two fluticasone products, Salmeterol, theophylline,

ipratropium/salbutamol and budesonide of which the average cost increased to R2 064.61± R00.00 per prescription.

- Asthma and COPD patients received the same items on their prescriptions for both 2008 and 2009. These were also the same prescriptions as the asthma received patients for the year 2009-2011 of which the cost was R1 274.17± R00.00 per prescription.

Since the patients' individual medication history was not available, the investigation into this observation falls outside the scope of this study.

4.6 CHAPTER SUMMARY

In this chapter, the results of the empirical investigation were outlined and discussed. The focus fell on the prevalence of prescribing patterns in asthma patients as well as the cost implications of COPD in asthma patients. The data was analysed according to gender, geographical areas, and the five age groups. The cost saving trough generic indicators were investigated as well as the influence of levies and third party payers on the average cost of asthma medicine items and prescriptions. The cost implications of gender and the five age groups on asthma medicine items and prescriptions were also highlighted. The influence of COPD as co-morbidity on asthma prescriptions and the cost implication thereof was noted.

In Chapter 5, the conclusions drawn from the study as well as recommendations and limitations are presented.

CHAPTER 5

CONCLUSIONS, LIMITIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

This chapter presents a number of conclusions regarding the literature study as well as the results obtained from the empirical study set out in Chapter 4. These conclusions are discussed in view of the objectives that were set in Chapter 1. The limitations of the study are noted and recommendations are made pertaining to possible future studies on the prescribing patterns of asthma medication.

5.2 CONCLUSIONS

Below are the conclusions drawn in light of the specific objectives that were set in Chapter 1. These conclusions are divided into two groups:

- Literature study conclusions
- Empirical research study conclusions

These two conclusions will be further discussed in detail.

5.2.1 Conclusions to the literature study

5.2.1.1 Objective one: *to review asthma severity as an illness with prevalence, risk factors and the treatment guidelines thereof.*

This was done through an extensive literature review in Chapter 2. Asthma was defined and classified by its clinical, physiological and pathological characteristics. The prevalence, risk factors and treatment guidelines associated with asthma were discussed.

This objective was addressed by means of the literature review presented in Chapter 2. Asthma was defined and classified in terms of its clinical, physiological and pathological

characteristics. The prevalence, risk factors and treatment guideline associated with asthma were considered.

The literature indicated that asthma is a complex disease with different levels of severity and treatment regimes. Globally, asthma affects approximately 300 million people according to the WHO survey (WHO, 2013b). South Africa's asthma prevalence is ranked 25th globally and affects 8.1% of the South African population (Masoli *et al.,* 2003:9). Asthma prevalence is, however, on the rise in South Africa and children and females are most susceptible to develop asthma according to the discussion in section 2.3. The literature also indicates that asthma is the eighth leading cause of disease burden in South Africa (Bradshaw *et al.,* 2007:2). The disease itself is made worse by risk certain factors, of which urbanisation, occupational hazards and viral infections are of importance in South Africa.

The pillars of asthma medication are anti–inflammatory and bronchodilator effects, and these are classified under bronchodilators and anti-asthmatics (see section 2.6 in Chapter 2). The bronchodilators help with quick relief in case of an asthma exacerbation. Drugs in this group include short-acting sympathomimetic agents, methylxanthines and anticholinergic agents (see table 2.8 in section 2.6). They are also known as "relievers". The anti-asthmatics are also known as "controllers" and comprise corticosteroids, leukotriene receptor antagonists and long-acting sympathomimetics (see table 2.8 in section 2.5). Anti-asthmatics are taken daily to control asthma and also to prevent asthma exacerbations.

Treatment guidelines have been developed to assist clinicians in deciding what the best treatment for patients would be. These constitute a key step in preventing, controlling and reducing complications arising from asthma. There is a wide range of guidelines; each with its own management plan and recommendations for treating asthma patients. However, without correct and timeous implementation, it is unlikely that the already high morbidity and mortality rates in South Africa will improve (Kathawaroo & Hukins, 2004:833).

5.2.1.2 **Objective two:** *to review asthma co-morbidities, especially COPD and the cost implication thereof*.

This objective was also addressed in the literature review in Chapter 2. The different co-morbidities associated with asthma were identified, defined and discussed accordingly. The most common co-morbidities associated with asthma include rhinitis, sinusitis, GORD, OSA, hormonal disorders and psychopathologies (see section 2.7 Chapter 2).

These co-morbidities all have a significant effect on the lives of asthma patients; however, none as great as COPD. COPD is the fourth leading cause of death and may soon surpass HIV/AIDS mortality rates in Africa (WHO, 2008b). While asthma mortality rates are significantly lower than COPD's (three million deaths), it is estimated that asthma accounts for 1 in every 250 deaths worldwide.

These chronic respiratory diseases are often no adequately diagnosed and are consequently inefficiently treated in sub-Saharan Africa (Van Gemert *et al.,* 2011:240). Having said that, it is also the case that asthma and COPD are not always easy to differentiate, but they have different treatment regimens (Miravitlles *et al.,* 2012:72). This situation may give rise to an increased risk of morbidity and mortality rates in asthma patients if the severity thereof is diagnosed incorrectly and an inadequate treatment plan is implemented. Such situations constitute further strains on the already overburdened healthcare sector of South Africa.

The conclusions regarding the empirical study are now presented.

5.2.2 Conclusions to the empirical study

5.2.2.1 Objective one: *to determine the prevalence of asthma from the year 2008 to 2011 stratified by age group, gender and geographical distribution in a section of the private healthcare sector of South Africa*.

The prevalence of asthma patients in the total population over the study period (January 2008 to December 2011) was 1.00%. The literature in Chapter 2 indicated a higher prevalence of asthma (8.1% of the South African population according to Masoli *et al.,* 2003:9). These differences in prevalence may be explained by the fact that the study only focused on asthma patient's register on the CDL and did not include patients who received acute medication for short term use. In terms of the number of patients, there was an increase from 2008 to 2009 and then a decrease from 2009 to 2011. These trends (namely the increase of asthma patients in 2008 to 2009, followed by the decrease from 2009 to 2011) reflect a broader the fluctuation of the total number of asthma patients throughout the different study parameters including the five different age groups, genders and geographical areas.

Five age groups were identified: age group 1 (AG1, 0-7 years), age group 2 (AG2, > 7- ≤ 18), age group 3 (AG3, > 18 ≤ 45 years), age group 4 (AG4, 45 ≤ 65 years) and age group 5

(AG5, 65 years and older). Prevalence regarding the different age groups was as follows: From table 4.10 it emerged that AG5 had the highest prevalence of asthma with 1.94%, while AG1 had the lowest prevalence (0.64%). This result was not consistent with the literature review which suggested that asthma is one of the most prevalent chronic diseases in children (see to section 2.3.2).

As far as gender is concerned, more female than male patients received asthma medication during the study period. In table 4.7, it could be seen that female patients had an asthma prevalence of 0.89% against the total female database while male patients had an asthma prevalence of 0.79% against the total male database. This situation could be attibruted to the hormonal disturbance in female patients (refer to section 2.3.1 and 2.4).

The geographical distributions of asthma patients revealed that KwaZulu-Natal had the highest prevalence of asthma (1.16%), followed by the Free State (1.03%) and the Western Province (0.97%) over the four year study period.

Asthma as a chronic disease, registered on the CDL, is not as prevalent in this section of the private healthcare sector of South Africa. A possible explanation for this finding can be that not all chronic asthma patients are currently registered on the CDL. From the above observations, possible risk factors for this specific study population are: the age of the patient (AG5), gender (females) and urbanisation. These factors seemed to have an influence on the prevalence of asthma. These results correlate with the trends found in the literature study, where it was found that gender (female) and urbanisation play an important role in the onset of asthma (Platts-Mills *et al.,* 2005:25; Boulet, 2009:900).

5.2.2.2 Objective two: *to investigate the influence of the gender and age on the prevalence of asthma prescriptions and items according to the database and the cost-implication thereof*

From the total database, asthma prescriptions represented 0.86% of the total number of prescription. Asthma medicine items, 0.49% consisted out of asthma medicine items on the total database. The number of prescriptions and the number of items per prescriptions increased from 2008 to 2009 followed by a decrease from 2009 to 2011. These trends were also reflected in the different gender and age groups number of prescriptions and number of asthma medicine items per prescription.

The average number of asthma prescriptions per year ranged from 8.28 ± 5.47 per patient in 2008 to 6.84 ± 7.54 per patient in 2011(see table 4.5). The average cost for an asthma prescription ranged from R263.46 ± R205.49 in 2009 to R322.12 ± R187.59 in 2011(see table 4.17). Furthermore, the average number of asthma items per prescription ranged from 1.55 ± 0.78 in 2008 to 1.37 ± 0.66 in 2009(see table 4.6). The average cost of a asthma medicine item ranged from R178.01 ± R131.91 in 2008 to 230.94 ± R140.88 in 2011(see table 4.20).

The average number of asthma prescriptions per year in terms of gender did not differ from the average values mentioned above. The average number of asthma prescriptions per patient per year also did not vary much between female and male patients (see table 4.8). Asthma prescriptions for females represented 57.98% of the total number of asthma prescriptions compared to the 42.01% for male patients during the study period.

The average cost of an asthma prescription did not differ greatly between genders or in terms of the general average cost per asthma prescription. For female asthma patients, the average cost per prescription was between R262.19 ± R207.00 in 2009 and R324.81 ± R190.44 in 2011. The average cost for an asthma prescription for male patients was between R265.23 ± 203.37 in 2009 and R318.53 ± 183.67 in 2011 (refer to table 4.26).

From table 4.8 in Chapter 4; the average number of asthma items on a prescription according to gender did not differ from the average values that are mentioned above. The average number of asthma items per prescription per patient also did not vary in terms of female and male asthma patients. Items prescribed for female patients represented a larger percentage (57.76%) than those for male asthma patients (42.24%) for the study period (refer to table 4.8). This can be explained by the fact that female patients represented a larger percentage of the total patient's population than males.

The average cost of an asthma medicine items in terms of gender also did not differ greatly from the average cost of an asthma medicine item. The average cost per asthma medicine was, however, slightly higher for female patients as compared to male patients. The average

cost for females' medicines ranged R179.52 ± R131.65 in 2008 to R234.35 ± R208.21 in 2011 and for males from R175.94 ± R149.96 in 2008 to R234.35 ± R208.21 in 2011(refer to table 4.27).

To conclude, then, gender did not have any significant influence on the prevalence and cost of asthma prescriptions and medicine items in this section of the private healthcare sector of South Africa.

In terms of age groups, the following emerged: From table 4.13 and 4.14 it can be concluded that patients in AG1, AG2 and AG3 received fewer prescriptions per year on average than the average number of prescriptions per year for the general asthma population. Patients in AG4 received the same average number of prescriptions per year as the general asthma population, while AG5 had a higher average number of prescriptions per year as compared to the general asthma population (refer to section 4.4.5).

From these observations it is clear that a decrease in the age groups brings about an increase in the average cost of an asthma prescription per patient in this study population. AG1 was prescribed more expensive medications than older patients in the other age groups.

Patients in AG1, AG2 and AG3 had a slightly higher average number of asthma medicine items per prescription than the general asthma population. Patients in AG4 had the same average number of asthma medicine items per prescription per patient per year as the general asthma population; while AG5 received a slightly lower number of asthma medicine items per prescription than the average asthma item on a prescription (refer to section 4.4.5).

One can conclude that an increase in age group also means an increase in the average number of asthma items on per patient, except when the age group is older than 65 years in which case a decrease in the average number of medicine items per prescription is likely (see tables 4.11 and 4.12).

From the above observations it is clear that a decrease in the age groups brings about an increase in the average cost of an asthma prescription. AG1 was prescribed more expensive prescriptions than older patients in the other age groups.

Patients in AG1, AG2 and AG3 had a slightly higher average number of asthma medicine items per prescription than the general asthma population. Patients in AG4 had the same

average number of asthma medicine items per prescription than the general asthma population; while AG5 had a slightly lower number of asthma medicine items per prescription than the average asthma prescription (refer to section 4.4.5).

The study can conclude that an increase in age group will also mean an increase in the average number of asthma items per prescription, except when the age group is older than 65 years which will causes a decrease in the average number of medicine items per prescription (refer to Table 4.11 and 4.12).

The average cost per asthma medicine item was highest for AG1 followed by AG2. The average medicine item cost of AG1 and AG2 was also higher than the average for items in the asthma group. AG4 had the lowest average cost per prescription per patient for the four year study period (see tables 4.31 and 4.32).

From the above it can be seen that a decrease in age group causes an increase in the average cost of an asthma medicine item in this study population. However, this is not the case for age groups over 65 years of age, where the average medicine cost tends to increase. Patients in AG1 and AG2 were prescribed more expensive drugs than patients in the other age groups. This could be ascribed that small children and paediatrics did not use generic products.

5.2.2.3 Objective three: *to determine the medicine costs of treating asthma from the year 2008 to 2011 according to age groups, gender and the cost incurred by the third-party payer as well as the patient in (levies) in a section of the private healthcare sector of South Africa.*

The asthma expenditures in this study only took into consideration the direct medicine cost incurred in the treatment of asthma. Hospitalisation and other indirect costs, which play an important role in the overall costs of asthma, were not included but could be useful in future studies. From the results and discussion in Chapter 4 (section 4.3.2 and 4.4.7.1) the following conclusions can be made:

It was found that asthma medicine cost accounted for 0.88% of the total medical expenditure (N = R8 766 090 670.39) in the study period (see table 4.4). The total cost of asthma medication as a percentage of the total medication cost showed a decrease from 2008 (1.02%) to 2011 (0.71%). The medical schemes paid 84.21% of the total asthma expenditure and patients were responsible for 15.79% of the total asthma expenditure (see table 4.16).

An explanation for this could be that asthma patients bought expensive asthma medication when an equivalent cheaper generic substation was actually available.

Asthma medication for AG2 represented 2.07% of the total expenditure, followed by AG1 with 1.69% of the total asthma expenditure. AG4 had the lowest total asthma expenditure, which constituted 0.75% of the total asthma expenditure for the study period (refer to table 4.28).

The total cost of asthma medication prescribed for female patients represented 1.03% and medication for male asthma patients represented 0.87% of the total cost of medications prescribed for the four year study period (see table 4.25) . Because female patients had a higher prevalence for asthma as compared with their male counterparts, the total cost for treating female asthma patients can be expected to be higher than for male patients. The difference in gender therefore contributes towards the difference in cost of treating asthma..

5.2.2.4 Objective four: *to determine the effect of generic substitution on the usage and cost of asthma treatment according to the database.*

From the results in table 4.19 it can be seen that the average cost of generic asthma items was lower than the original asthma product over the study period. However, asthma products without generic equivalents “N” represented the highest average cost per asthma items and were also the most prescribed generic indicators over the study period. The result indicated that products without a generic indicator “N” represented a total cost 78.62% over the study period (see table 4.23).

The possible cost saving, if generic substitutions “Y” were used instead of the original product “O”, could have led to the following

- R618 315.92 (46.97%, N = R1 317 609.02) throughout 2008.
- R909 156.88 (47.96%, N = R1 895 466.40) during 2009.
- R3 290 732.98 (67.55% N =R 4 8718 70.26) throughout 2010.
- R1 008 518.83 (40%; N = R2 499 919.15) during 2011 (Refer to table 4.24).

The difference in the average cost of original and average cost of generic items showed a statistical significance ($p \leq 0.05$) and a high to medium practical significance in this section of the private healthcare sector. This can be an indication that generic substitutions of asthma products are still under-utilised.

5.2.2.5 Objective five: *to investigate the prevalence of COPD in asthma patients and the cost-implication thereof.*

Chronic respiratory diseases like asthma and COPD are associated with enormous healthcare expenditures (Bradshaw *et al.,* 2007:439). There is a great need to undertake studies that explore the financial burden of COPD on asthma patients. The influence of COPD together with asthma is discussed below with reference to prescription and cost of medication. Prescriptions containing one medicine item were the most prevalent for both asthma and asthma-COPD patients. When more items were prescribed, the number of prescriptions declined. However, when the number of items increased on the prescription, the average cost of the prescription also increased (refer to section 4.5.2).

The most frequently single prescribed asthma medication item was fluticasone (n = 39 721), whereas theophylline (n = 17 657) was the most prescribed single asthma-COPD medication over the study period. The average prescription cost for patients with asthma-COPD was higher throughout the study period than those for patients suffering from asthma only. The CPI for single asthma items was calculated as 0.98, which indicates there was equilibrium between cost percentage and prevalence percentage (number of prescriptions). The CPI for asthma-COPD over the four year study period was calculated as 1.04, which indicates that asthma-COPD single items are relatively more expensive than single asthma items per prescription over the four year study period (refer to table 4.33).

Two or more medicine items per prescription indicate a more severe asthma condition and treatment tends to consist of more controller medications being prescribed. The most prevalent two asthma medicine items prescribed were fluticasone and montelukast (n = 4604). Asthma with COPD as co-morbidity usually had a reliever (fluticasone, budesonide) together with theophylline. The CPI for two asthma medicine items per prescription was calculated to be 0.94 and is less expensive than the asthma-COPD prescriptions containing two medicine items per prescription. While asthma-COPD prescriptions containing two medicine items, had a calculated CPI value of 1.16 over the four year study period which correlates with the above statement, mentioning these prescriptions were more expensive (refer to table 4.34).

Prescriptions containing three medicine items per prescription resulted in the increase of the average cost per prescription. The amount of these three item prescriptions decreased when compared to prescriptions only containing one medicine item. These trends were seen both in asthma and asthma-COPD patients. Prescriptions containing three medicine items for

asthmatics usually comprised out of two anti-asthmatics (fluticasone, montelukast) and a bronchodilator (salbutamol). Prescriptions containing three medicine items for asthma-COPD sufferers usually had tiotropium and theophylline with an inhaled corticosteroid (fluticasone). The CPI calculated over the four year study period for asthma-COPD was 1.19 and indicted that these prescriptions were more expensive when compared to the CPI of three items per prescription for asthma alone, which was calculated to be 0.91 over the four year study period (refer to table 4.34). Prescriptions containing four to eight items were also analysed. The same trends were found in terms of the cost and prevalence for both asthma and asthma-COPD patient. However, there were too few observations to arrive at an accurate conclusion (see tables 4.35 – 4.40).

To conclude the discussion of the economic burden of asthma and asthma-COPD in patients, it can be postulated that as the number of items on a prescription increases, so does the average cost of the prescription. However, when the number of items on a prescription increased a decrease in the total number of those specific prescriptions in the database was found.

From the above observations it is clear that there is a difference between the cost of asthma and the cost of asthma-COPD, with asthma-COPD always being the more expensive one. This finding confirms the notion that prescriptions with the same number of items are more expensive for asthma-COPD patients than for asthma patients without COPD as co-morbidity. This conclusion correlates with the literature study conducted in order to address objective two where it was found that COPD increases an asthma patient's economic burden (Van Ganse *et al.,* 2006:144).

5.3 LIMITATIONS OF THE STUDY

There were a few limitations that had a bearing on the study and the accuracy thereof. The following limitations should be considered:

- The data for analysis were obtained from one medicine claims database only, therefore the can results only be generalised to the allocated portion of the private healthcare sector of South Africa.
- All data entered into the database were considered to be correct from the PBM and the data were analysed from this perspective.

- Only direct cost of medication was included because hospitalisation costs were not available from the database, therefore the monetary medical burden of asthma could not be determined comprehensively.
- The database did not contain any specific information on which disease came first; asthma or COPD.
- The study only made use of data from the private healthcare sector of South Africa, and therefore the economic burden of asthma on the total South African population could not be determined.

5.4 RECOMMENDATIONS

The following recommendations can be made to aid future studies regarding asthma management in South Africa:

- The geographical distribution of asthma should be further investigated. The risk factors should also be considered as a basis for the prevalence of asthma in the different provinces.
- The total cost of asthma including hospitalisation cost must be ascertained in order to determine the economic burden of asthma more accurately.
- The influence of generic substation of different asthma medications should be further investigated.
- The prevalence of asthma should be consistently monitored, especially in female patients and adults older than 65 years.

5.5 CHAPTER SUMMARY

In this chapter, the conclusions that were drawn from the literature and empirical research study were presented. A number of limitations involved in the study were also mentioned and recommendations were made for future research in the field.

REFERENCES LIST

AAAAI (American Academy of Allergy Asthma & Immunology). 2010. Asthma. http://www.aaaai.org/conditions-and-treatments/conditions-a-to-z-search/asthma.aspx Date of access: 2 Jun. 2012.

Acock, A.C. & Stavig, G.R. 1979. A measure of association for nonparametric statistics .*Journal of social forces,* 57(4):1381-1386.

Agbetile, J. & Green, R. 2011. New therapies and management strategies in the treatment of asthma: patient-focused developments. *Journal of asthma and allergy,* 4(1):1-12.

Aït-Khaled, N., Enarson, D. Bousquet, J. 2001. Chronic respiratory disease in developing countries: the burden and strategies for prevention and management. *Bulletin of the World Health Organization,* 79(10):971-979.

Ait-Khaled, N., Odhiambo., N, Pearce, N., Adjoh, K.S., Maesano, I.A., Benhabyles, B., Bouhayad, Z., Bahati, E., Camara, L., Catteau, C., El Sony, A., Esamai, F.O., Hypolite, I.E., Melaku, K., Musa, O.A., Ng'ang'a, L., Onadeko, B.O., Saad, O., Jerray, M., Kayembe, J.M., Koffi, N.B., Khaldi, F., Kuaban, C., Voyi,K., M'Boussa, J., Sow, O., Tidjani, O. & Zar, H.J. 2007. Prevalence of symptoms of asthma rhinitis and eczema in 13- to 14- year- old children in Africa: the International Study of Asthma and Allergies in Childhood Phase III. *Allergy journal,* 62(3):247-258.

Al-Alawi, A., Ryan, C.F., Flint, J.D. & Müller, N.L. 2005. Aspergillus-related lung disease. *Canadian respiratory journal,* 12(7):377-387.

Alam, M., Barzilai, D.A. & Wrone, D.A. 2005. Confidence intervals in procedural dermatology: an intuitive approach to interpreting data. *Dermatologic surgery,* 31(4):462-466.

Al-Busaidi, N.H., Habibullah, Z. & Soriano, J.B. 2013. The asthma cost in Oman. *Sultan Qaboos University medical journal,* 13(2):218-223.

Allua, S. & Thompson, C.B. 2009. Inferential Statistics. *Air medical journal,* 28(4):168-171. Almqvist, C., Worm, M. & Leynaert, B. 2008. Impact of gender on asthma in childhood and adolescence: a GA^{2}LEN review. *Allergy journal,* 63(1):47-57. Anandan, C., Nurmatov U., van Schayck, O.C.P. & Sheikh, A. 2010. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy journal,* 65(1):152- 167.

Anderson, M. & Thomas, D.A. 2010. Drug therapy for chronic asthma in children. *Archives of disease in childhood. Education and practice edition,* 95(5):145-150.

Anis, A.H., Carruthers, S.G., Carter, A.O. & Kierulf, J. 1996. Variability in prescription drug utilization: issues for research. *Canadian Medical Association journal,* 154(5):635-640.

Ansel, H.C. 2010. Pharmaceutical calculations. 13th ed. Georgia: University of Georgia. 444p.

Apter, A.J. 2012. Advances in adult asthma diagnosis and treatment and health outcomes, education, delivery and quality in 2011: what goes around comes around. *The journal of allergy and clinical immunology,* 129(1):69-75.

Armstrong, D., Marshall, J.K., Chiba, N., Enns,R., Fallone, C.A., Fass, R., Hollingworth, R., Hunt, R.H., Kahrilas, P.J., Mayrand, S., Moayyedi, P., Paterson, W.G., Sadowski, D. & van Zanten, S.J.O. 2005. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults: – update 2004. *Canadian journal of gastroenterology,* 19(1):15-35.

Arshad, S.H. 2010. Does exposure to indoor allergens contribute to the development of asthma and allergy? *Current allergy and asthma reports,* 10(1):49-55.

Asadoorian, M.O. & Kantarelis, D. 2005. Essentials of inferential statistics. 4th ed. Lanham, MD:Maryland. 279p.

Asher, M.I., Montefort, S., Björkstén, B., Lai, C.K.W., Strachan, D.P., Weiland, S.K., Williams, H. 2006. Worldwide time trend in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phase One and Three repeat multicounty cross-sectional surveys. *Lancet,* 368(9537):733-743.

Bacharier, L.B., Boner, A., Carlsen, K.H., Eigenmann, P.A., Frischer, T., Götz, M., Helms, P.J., Hunt, J., Liu, A., Papadopoulos, N., Platts-Mills, T., Pohunek, P., Simons, F.E.R.,

Valovirta, E., Wahn, U. & Wildhaber, J. 2008. Diagnosis and treatment of asthma in Childhood: a PRACTALL consensus report. *Allergy journal,* 65(1):5-34.

Bahadori, K., Doyle-Waters, M.M., Marra, C., Lynd, L., Alasaly, K., Swiston, J. & FitzGerald, J.M. 2009. Economic burden of asthma: a systematic review. *BMC pulmonary medicine,* 9(24):1-16.

Barbi, E. & Longo, G. 2007. Chronic and recurrent cough, sinusitis and asthma. Much ado about nothing. *Pediatric allergy and immunology,* 18(18):22-24.

Barnes, P.J. 2004. The size of the problem of managing asthma. *Respiratory medicine,* 98(2):4-8.

Barnett, S.B.L. & Nurmagambetov, T.A. 2011. Costs of asthma in the United States: 2002-2007. *The journal of allergy and clinical immunology,* 127(1):145-152.

Bateman, E., Feldman, C., Mash, R., Fairall, L., English, R. & Jithoo, A. 2009. Systems for the management of respiratory disease in primary care – an international series: South Africa. *Primary care respiratory journal,* 18(2):69-75.

Bateman, E.D., Hurd, S.S., Barnes, P.J., Bousquet, J., Drazen, J.M., FitzGerald, M., Gibson, P., Ohta, K., O'Byrne, P.J., Pedersen, S.E., Pizzichini, E., Sullivan, S.D., Wenzel, S.E. & Zar H.J. 2008. Global strategy for asthma management and prevention: GINA executive summary. *The European respiratory journal,* 31(1):143-178.

Bateman, E.D., Reddel, H.K., Eriksson, G., Peterson, S., Östlund, O., Sears, M.R., Jenkins, C., Humbert, M., Buhl, R., Harrison, T.W., Quirce, S. & O'Byrne, P.M. 2010. Overall asthma control: the relationship between current control and future risk. *The journal of allergy and clinical immunology,* 125(3):600-608.

Bayram, H., Sapsford, R.J., Abedelaziz, M.M. & Khair, O.A. 2001. Effect of ozone and nitrogen dioxide on the release of proinflammatory mediators from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients in vitro. *The journal of allergy and clinical immunology,* 107(2):287-294.

Beasley, R., Crane, J., Lai, C.K.W. & Pearce N. 2000. Prevalence and etiology of asthma. *The journal of allergy and clinical immunology,* 105(2):466-472.

Beasly, R., Keil, U., von Mutius, E. & Pearce, N. 1998. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The

International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet,* 351(9111):1225-1232.

Bellia, V., Pedone, C., Catalano, F., Zito, A., Davi, E., Palange, S., Forastiere, F. & Incalzi, R.A. 2007. Asthma in the elderly: mortality rate and associated risk factors for mortality. *Chest journal,* 132(4):1175-1182.

Biau, D.J., Kernéis, S. & Porcher, R. 2008. Statistics in brief: the importance of sample size in the planning and interpretation of medical research. *Clinical orthopaedics and related research,* 466(9):2282-2288.

Blackman, J.A. & Gurka, M.J. 2007. Development and behavioral comorbidities of asthma in children. *Journal of developmental and behavioral pediatrics,* 28(2):92-99.

Bosley, C.M., Corden, Z.M. & Cochrane, G.M. 1996. Psychosocial factors and asthma. *Respiratory medicine,* 90(8):453-457.

Boulet, L.P. 2009. Influence of comorbid conditions on asthma. The *European respiratory journal,* 33(4):897-906.

Boulet, L.P. 2013. Asthma and obesity. *Clinical and experimental allergy,* 43(1):8-21.

Boulet, L.P. & Boulay M.E. 2011. Asthma-related comorbidities. *Expert review of respiratory medicine,* 5(3):377-393.

Boulet, L.P., Mclvor, R.A. & Marciniuk, D. 2007. Respiratory guidelines implementation in Canada. *Canadian respiratory journal,* 14(6):329-330.

Bousquet, J. 1998. Allergic rhinitis: review of the guidelines. *Revue Francaise d'Allergolgie et d'Immunologie Clinique,* 38(10):938-941.

Bousquet, J. Clark, T.J.H., Hurd, S., Khaltaev, N., Lenfant, C., O'Byrne, P. & Sheffer, A. 2007. GINA guidelines on asthma and beyond. *Allergy journal,* 62(2):102-112.

Bousquet, J., Godard, P. & Grouse, L. 2006. Global integrated guidelines are needed for respiratory diseases. *Primary care respiratory journal,* 15(1):10-12.

Bousquet, J., Mantzouranis, E., Cruz, A.A., Aït-Khaled, N., Baena-Cagnani, C.E., Bleecker, E.R., Brightling, C.E., Burney, P., Bush, A., Busse, W.W., Casale, T.B., Chan-Yeung, M., Chen, R., Chowdhury, B., Chung, K.F., Dahl, R., Drazen, J.M., Fabbri, L.M., Holgate, S.T., Kauffmann, F., Haahtela, T., Khaltaev, N., Kiley, J.P., Masjedi, M.R., Mohammed, Y.,

O'Byrne, P., Patridge, M.R., Rabe, K.F., Togias, A., van Weel, C., Wenzel, S., Zhong, N. & Zuberbier, T. 2010. Uniform definition of asthma severity, control and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *The journal of allergy and clinical immunology,* 126(5):926-938.

Bousquet, J., Ndiaye, M., Aït–Khaled, N., Annesi–Maesano, I. & Vignola, A.M. 2003. Management of chronic respiratory and allergic diseases in developing countries. Focus on sub–Saharan Africa. *Allergy journal,* 58(4):265-283.

Bradshaw, D., Norman, R. & Schneider, M. 2007. A clarion call for action based on refined DALY estimates for South Africa. *South African medical journal,* 97(6):438-439. Braman, S.S. 2006. The global burden of asthma. *Chest journal,* 130(1):4-12.

Brandt, S., Gale, S. & Tager, I. 2012. The value of health interventions: evaluating asthma case management using matching. *Applied economics,* 44(17):2245-2263.

Bresciani, M., Paradis, L., Des Roches, A., Vernhet, H., Vachier, I., Godard, P., Bousquet, J. & Chanez, P. 2001. Rhinosinusitis in severe asthma. *The journal of allergy and clinical immunology,* 107(1):73-80.

Broder, S., Hoffman, S.L. & Hotez, P.J. 2002. Cures for the third world's problems: the application of genomics to the diseases plaguing the developing world may have huge medical and economic benefits for those countries and might even prevent armed conflict. *European Molecular Biology Organization report,* 3(9):806-812.

Brodie, D.C. & Smith, W.E. 1979. Constructing a conceptual model of drug utilization review. *Hospitals,* 50(6):143-144.

Bryant-Stephens, T. 2009. Asthma disparities in urban environments. *The journal of allergy and clinical immunology,* 123(6):1199-1206.

Burney, P.G.J., Luczynska, C., Chinn, S. & Jarvis, D. 1994. The European Community Respiratory Health Survey. *The European respiratory journal,* 7(5):954-960.

Burr, M.L., Limb, E.S., Andrae, S., Barry, D.M. & Nagel F. 1994. Childhood asthma in four countries: a comparative study. *International journal of epidemiology,* 23(2):341-347.

Bush, A. & Zar, H.J. 2011. WHO universal definition of severe asthma. *Current opinion in allergy and clinical immunology,* 11(2):115-121.

Campos, H.D.S & Lemos, A.C. 2009. Asthma and COPD according to the pulmonologist. *Jornal brasileiro de pneumologia*, 35(4):301-309.

Carlin, J.B. & Doyle, L.W. 2001. Statistics for clinicians. 4: basic concepts of statistical reasoning: hypothesis test and the t-test. *Journal of paediatrics and child health,* 37(1):72-77.

Carlsen, K.H. & Carlsen, K.C. 2008. Respiratory effects of tobacco smoking on infants and young children. *Paediatric respiratory reviews,* 9(1):11-20.

CEPA (California Environmental Protective Agency). 2006. Environmental Tobacco Smoke: A toxic air contaminant fact sheet. *www.arb.ca.gov/toxics ets factsheetets.pdf* Date of access: 26 Apr. 2013.

Chipps, B.E . 2008. Asthma in infants and children. *Clinical cornerstone,* 8(4):44-61.

Chipps, B.E., Zeiger, R.S., Dorenbaum, A., Borish, L., Wenzel, S.E., Miller, D.P., Hayden, M.L., Bleecker, E.R., Simons, F.E.R., Szefler, S.J., Weiss, S.T. & Haselkorn, T. 2012. Assessment of asthma control and asthma exacerbations in the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) observational cohort. *Current respiratory care report,* 1(4):259-269.

Cho, S.H. 2010. Pharmacogenomic approaches to asthma treatment. *Allergy, asthma & immunology research,* 2(3):177-182.

Clark, N.M., Dodge, J.A., Shah, S., Thomas, L.J., Andridge, R.R. & Awad, D. 2010. A current picture of asthma diagnosis, severity, control and medication use in low income minority preteens. *The journal of asthma,* 47(2):150-155.

CMS (Council for Medical Schemes). 2013a. Asthma. http://www.medicalschemes.com/ Date of access: 22 Feb. 2013.

CMS (Council for Medical Schemes). 2013b. Prescribed minimum benefits. http://www.medicalschemes.com/medical_schemes_pmb/index.htm Date of access: 25 Nov. 2013.

Cohen, J. 1988. Statistical power analysis for behavioral sciences 2nd ed. Hillsdale, N.J.:Lawrence Erlbaum associates, inc. 567p.

Comer, J.S., Pincus, D.B. & Hofmann, S.G. 2012. Generalized anxiety disorder and the proposed associated symptoms criterion change for DSM-5 in a treatment-seeking sample of anxious youth. *Depression and anxiety,* 29(12):994-1003.

Cowl, C.T. 2011. Occupational asthma: review of assessment, treatment and compensation. *Chest journal,* 139(3):674-681.

Cruz, A.A., Popov, T., Pawankar, R., Annesi-Maesano, I., Fokkens, W., Kemp, J., Ohta, K., Price, D. & Bousquet, J. 2007. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy journal,* 62(84):1-41.

Czerwinski, S., Gollero, J., Qiu, C., Sorensen, T.K. & Williams, M.A. 2012. Migraine-asthma comorbidity and risk of hypertensive disorders of pregnancy. *Journal of pregnancy,* 1(1):1-8.

D'Amato, G. 2011. Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma. *Multidisciplinary respiratory medicine,* 6(1):28-37.

D'Amato, G., Baena-Cagnani, C.E., Cecchi, L., Annesi-Maesano, I., Nunes, C., Ansotequi, I., D'Amato, M., Liccardie, G., Sofia, M. & Canonica, W.G. 2013. Climate change, air pollution and extreme events leading to increasing prevalence of allergic respiratory disease. *Multidisciplinary respiratory medicine,* 8(12):1-9.

D'Amato, G., Cecchi, L., D'Amato, M. & Liccardi, G. 2010. Urban air pollution and climate change as environmental risk factors of respiratory allergy: an update. *Journal of investigational allergology and clinical immunology,* 20(2):95-102.

Dalgaard, P. 2008. Introductory Statistics with R. 2nd. University of Copenhagen: Denmark. 370p.

De Groot, E.P., Duiverman, E.J. & Brand, P.L . 2010. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *The European respiratory journal,* 36(3):671-679.

Dennis, R.J., Solarte, I. & Rodrigo, G. 2008. Asthma in adults. *British medical journal,* 1(1):1-47.

Diette, G.B., McCormack, M.C., Hansel, N.N., Breysse, P.N. & Matsui, E.C. 2008. Environmental issues in managing asthma. *Respiratory care,* 53(5):602-617.

Dixon, A.E., Clerisme-Beaty, E.M., Sugar, E.A., Cohen, R.I., Lang, J.E., Brown, E.D., Richter, J.E., Irvin C.G. and Mastronarde, J.G. 2011. Effects of obstructive sleep apnea and gastroesophageal reflux disease on asthma control in obesity. *The journal of asthma,* 48(7):707-713.

Donath, S., Davidson, A. & Babl. 2013. A primer for clinical researchers in the emergency department: Part V: How to describe data and basic medical statistics. *Emergency medicine Australasia,* 25(1):13-21.

Du Plessis, J.M., Gerber, J.J. and Brand, L. 2013. Managing asthma in primary care through imperative outcomes. *Journal of evaluation in clinical practice,* 19(2):235-242.

Du Prel, J.B., Röhrig, B., Hommel, G. & Blettner, M. 2010. Choosing statistical test: part 12 of a series on evaluation of scientific publications, *Deutsches Ärzteblatt international,* 107(19):343-348.

Duffy, D.L. 1997. Genetic epidemiology of asthma. *Epidemiology reviews,* 19(1):129-143.

Ehrlich, R.I., Du Toit, D., Jordaan, E., Volmink, J.A., Weinberg, E.G. & Zwarenstein M. 1995. Prevalence and reliability of asthma symptoms in primary school children in Cape Town. *International journal of epidemiology,* 24(6):1138-1145.

Ehrlich, R.I., White, N., Norman, R., Laubscher, R., Steyn, K., Lombard, C. & Bradshaw, D. 2005. Wheeze, asthma diagnosis and medication use: a national adult survey in a developing country. *Thorax,* 60(11):895-901.

Eisner, M.D., Yelin, E.H., Katz, P.P., Earnest, G. & Blanc, P.D. 2002. Exposure to indoor combustion and adult asthma outcomes: environmental tobacco smoke, gas stoves, and wood smoke. *Thorax,* 57(11):973-978.

El Ftouh, M., Yassine, N., Benkheder, A., Bouacha, H., Nafti, S., Taright, S., Fakhfakh, H., Ali-Khoudja, M., Texier, N. & El Hasnaoui, A. 2009. Paediatric asthma in North Africa: The Asthma Insights and Reality in the Maghreb (AIRMAG) study. *Respiratory medicine,* 103(2):S21-S29.

El-Ghitany, E.M. & Abd El-Salam, M.M. 2012. Environmental intervention for house dust mite control in childhood bronchial asthma. *Environmental health and prevention medicine,* 17(5):377-384.

Enarson, D.A. 2004. The hidden epidemic: chronic obstructive pulmonary disease. *The international journal of tuberculosis and lung disease,* 8(2):157-158.

English, R.G., Fairall, L.R. & Bateman, E.D. 2007. Keeping allergy on the agenda: integrated guidelines for respiratory disease in developing countries. *Allergy journal,* 62(3):224-229.

Esterhuizen, T.M., Hnizdo, E. & Rees, D. 2001. Occurrence and causes of occupational asthma in South Africa – results from SORDSA's Occupational Asthma Registry, 1997-1999. *South African medical journal,* 91(6):509-513.

Feng, M., Yang, B., Zhuang, Y., Yanagi, U. & Cheng. X.J. 2012. A study on indoor environment contaminants related to dust mite in dwellings of allergic asthma patients and of healthy subjects. *Bioscience trends,* 6(1):7-9.

Fedor-Freybergh, P.G. & Mikulecky, M. 2005. From the descriptive towards inferential statistics: hundred years since conception of the Student's t-distribution. *Neuro endocrinology letters,* 26(3):167-171.

Fulda, T.R., Lyles, A., Pugh, M.C. & Christensen, D.B. 2004. Current status of prospective drug utilization review. *Journal of managed care pharmacy,* 10(5):433-441.

Fung, V., Tager, I.B., Brand, R., Newhouse, J.P. & Hsu, J. 2008. The impact of generic-only drug benefits on patients' use of inhaled corticosteroids in a Medicare population with asthma. *BMC health services research,* 8(151):1-10.

Gaga, M., Zervas, E., Grivas, S., Castro M. & Chanez, P. 2007. Evaluation and management of severe asthma. *Current medical chemistry,* 14(9):1049-1059.

Garal, A., Liptsitz, J.D., Muhsen, K. & Gross, R. 2011. Depressive symptoms, risk factors and sleep in asthma: result from a national Israeli health survey. *General hospital psychiatry,* 34(1):17-23.

Gehring, U., Heinrich, J. Jacob, B., Richter, K., Fahlbusch, B., Schlenvoigt, G., Bischof, W. & Wichmann, H.E. 2001. Respiratory symptoms in relation to indoor exposure to mite and cat allergens and endotoxins. Indoor Factors and Genetics in Asthma (INGA) Study Group. *The European respiratory journal,* 18(3):555-563.

Gershon, A.S., Gaun, J. Wang, C. Victor, J.C. & To, T. 2012. Describing and quantifying asthma comorbidity: a population study. *Plos one* 7(5):1-12.

Gershon, A.S., Wang, C., Guan, J. & To, T. 2010. Burden of comorbidity in individuals with asthma. *Thorax,* 65(7):612-618.

Gibson, P. G., McDonald, V.M. & Marks, G.B. 2010. Asthma in older adults. *Lancet,* 4(376):803-813.

Gibson, P.G. & Simpson, J.L. 2009. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax,* 64(8):728-735.

Gilliland, F.D. 2009. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. *Pediatrics,* 123(3):S168-S173.

GOLD (Global Initiative for Chronic Obstructive Lung Disease). 2006. Global Strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. http://www.goldcopd.org/ Date of access: 10 Jun. 2013.

Gomulka, K. & Szczepaniak, W. 2012. Problem of depression in patients with bronchial asthma. *Pneumnologia I alergologia polska,* 80(4):317-322.

Goral A., Lipsitz., J.D., Muhsen., K. & Gross, R. 2012. Depressive symptoms, risk factors and sleep in asthma: results from a national Israeli health survey. *General hospital psychiatry,* 34(1):17-23.

Green, R.J. 2011. Pediatric asthma in Southern Africa. *The open allergy journal,* 4(1):8-15.

Green, R.J., Davis, G. & Price, D. 2008. Perceptions, impact and management of asthma in South Africa: a patient questionnaire study. *Primary care respiratory journal,* 17(4):212-216.

Green, R.J., Greenblatt, M.M., Plit, M., Jones, S. & Adam, B. 2001. Asthma management and perceptions in rural South Africa. *Annals of allergy, asthma and immunology,* 86(3):343-347.

Green, R.J., Zar, H.J. & Bateman, E.D. 2007. Asthma - is survival good enough? *South African medical journal,* 97(3):172-174.

Grimsley, L.F., Chulada, P.C., Kennedy, S., White, L., Wildfire, J., Cohn, R.D., Mitchell, H., Thornton, E., El-Dahr, J., Mvula, M.M. Sterling, Y., Martin, J.W., Stephans, K.U. & Lichtveld, M. 2012. Indoor environmental exposures for children with asthma enrolled in the HEAL study, Post-Katrina New Orleans. *Environmental health perspectives,* 120(11):1600-1606.

Guo, J.J., Gibson, J.T., Hancock, G.R. & Barker, K.N. 1995. Retrospective drug utilization review and the behavior of Medicaid prescribers: an empirical marginal analysis. *Clinical therapeutics,* 17(6):1174-1187.

Gupta, S.K. 2012. The relevance of confidence interval and *p*-value in inferential statistics. *Indian journal of pharmacology*, 44(1):143-144.

Guyatt, G., Jaeschke, R., Heddel, N., Cook, D., Shannon, H. & Walter, S. 1995. Basic statistics for clinicians: 1. Hypothesis testing. *Canadian Medical Association journal,* 152(1):27-32.

Guyatt, G., Jaeschke, R., Heddel, N., Cook, D., Shannon, H. & Walter, S. 1995. Basic statistics for clinicians: 2. Interpreting study results: confidence intervals. *Canadian Medical Association journal,* 152(2):169-173.

Hakola, R., Kauppi, P., Leino, T., Ojajärvi, A., Oksanen, T., Haahtela, T., Kivimäki, M. & Vahtera, J. 2011. Persistent asthma, comorbid conditions and the risk of work disability; a prospective cohort study. *Allergy journal,* 66(12):1598-1603.

Halbert, R.J. & Isonaka, S. 2006. International Primary Care Respiratory Group (IPCRG) Guidelines: integrating diagnostic guidelines for managing chronic respiratory diseases in primary care. *Primary care respiratory journal,* 15(1):13-19.

Haldar, P. & Pavord, I.D. 2012. Diagnosis and management of adult asthma. *Journal of medicine,* 40(5):243-251.

Haldar, P., Pavord, I.D., Shaw, D.E., Berry, M.A., Thomas, M., Brightling, C.E., Wardlaw, A.J. & Green, R.H. 2008. Cluster analysis and clinical asthma phenotypes. *American journal of respiratory and critical care medicine,* 178(3):218-224.

Hales, B.J., Martin, A.C., Pearce, L.J., Laing, I.A., Hayden, C.M., Goldblatt, J., Le Souëf, P.N. & Thomas, W.R. 2006. IgE and IgG anti-house dust mite specificities in allergic disease. *The journal of allergy and clinical immunology,* 118(2):361-367.

Hanania, N.A., King, M.J, Braman, S.S., Saltoun, C., Wise, R.A., Enright, P., Falsey, A.R., Mathur. S.K., Ramsdell, J.W., Rogers, L., Stempel, D.A., Lima, J.J., Fish, J.E., Wilson, S.R., Boyd, C., Patel, K.V., Irvin, C.G., Yawn, B.P., Halm, E.A., Wasserman, S.I., Sands, M.F., Ershler, W.B. & Ledford, D.K. 2011. Asthma in the elderly: current understanding and future research need: a report of a National Institute on Aging (NIA) workshop. *The journal of allergy and clinical immunology,* 128(3):S4-S24.

Hargreave, F.E. & Nair, P. 2009. The definition and diagnoses of asthma. *Clinical & experimental allergy,* 39(11):1652-1658.

Hashimoto, S. & Bel, E.H. 2012. Current treatment of severe asthma. *Clinical and experimental allergy,* 42(5):693-705.

Heinrich, J. 2011. Influence of indoor factors in dwellings on the development of childhood asthma. *International journal of hygiene and environmental health,* 214(1):1-25.

Holgate, S.T. 2011. Asthma: a simple concept but in reality a complex disease. *European journal of clinical investigation*, 41(12):1339-1352.

Holguin, F. Bleecker, E.R., Busse, W.W., Calhoun, W.J., Castro, M., Erzurum, S.C., Fitzpatrick, A.M., Gaston, B., Israel, E., Jarjour, N.N., Moore, W.C., Peters, S.P., Yonas, M.,Teague, W.G. Wenzel, S.E. 2011. Obesity and asthma: an association modified by age of asthma onset. *Journal of allergy and clinical immunology,* 127(6):1486-1493.

Holley, A.D. & Boots, R.J. 2009. Review article: management of acute severe and near-fatal asthma. *Emergency medicine Australasia,* 21(4):259-268.

Horne, R. 2006. Compliance, adherence and concordance: implication for asthma treatment. *Chest journal*, 130(1):65-72.

IPCRG (International Primary Care Respiratory Group). 2008. Asthma guidelines 2008. https://www.theipcrg.org/display/RESAST/Asthma+Guidelines+2008 Date of access: 20 May 2013.

Jackson, R. & Feder, G. 1998. Guidelines for clinical guidelines. A simple, pragmatic strategy for guideline development. *British medical journal,* 317(7156):427-428.

Jafta, N., Batterman, S.A., Gqaleni, N., Naidoo, R.N. & Robins, T.G. 2012. Characterization of allergens and airborne fungi in low and middle-income homes of primary school children in Durban, South Africa. *American journal of industrial medicine,* 55(12):1110-1121.

Jie, Y., Ismail, N.H., Jie, X. & Isa, Z.M. 2011. Do indoor environments influence asthma and asthma related symptoms among adults in homes?: a review of the literature. *Journal of the Formosan Medical Association,* 110(9):555-563.

Kallstrom, T.J. 2004. Evidence-based asthma management. *Respiratory care,* 49(7):783-792.

Kathawaroo, S. & Hukins, G. 2004. Asthma management in practice. *South African medical journal,* 94(10):832-833.

Katon, W.J., Richardson, L., Lozano, P. & McCauley, E. 2004. The relationship of asthma and anxiety disorders. *Psychosomatic medicine,* 66(3):349-355.

Katsnelson, M.J., Peterlin, B.L., Rosso, A.L., Alexander, G.M. & Erwin, K.L. 2009. Self-reported vs measured body mass indices in migraineurs. *Headache,* 49(5):663-668.

Keller, G. 2012. Managerial Statistics. 9th ed. Ontario, Canada:Wilfred Laurier University. 921p.

Keller, M.B. & Lowenstein, S.R. 2002. Epidemiology of asthma. *Seminars in respiratory and critical care medicine,* 23(4):317-329.

Kent, B.D. & Lane, S.J. 2012. Twin epidemics: asthma and obesity. *International archives of allergy and immunology,* 157(3):213-214.

Kilian, P.J. 2005. The treatment of asthma: a managed pharmaceutical care approach. Potchefstroom: North-West University. (Dissertation – M.Pharm). 171 p.

Kim, C.Y., Park, H.W., Ko, S.K., Chang, S.I., Moon, H.B., Kim, Y.Y. & Cho, S.H. 2011. The financial burden of asthma: a nationwide comprehensive survey conducted in the republic of Korea. *Allergy, asthma & immunology research,* 3(1):34-38.

Kling, S. 2007. Severe asthma and acute attacks: diagnosis and management in adults and children. *The South African family practice,* 49(5):36-40.

Kling, S., Zar, H.J., Levin, M.E., Green, R.J., Jeena, P.M., Risenga, S.M., Thula, S.A. & Goussard, R.P. 2013. March 2013. Guidelines for the management of acute asthma in children: 2013 update. *South African medical journal,* 103(3):199-207.

Kupczyk, C. & Wenzel, S. 2012. U.S. and European severe asthma cohorts: what can they teach us about severe asthma? *Journal of internal medicine,* 272(2):121-132.

Kusuoka, H. & Hoffman, J.I. 2002. Advice on statistical analysis for Circulation Research. *Circulation research,* 91(8):662-671.

Kwok, M.Y., Walsh-Kelly, C.M., Gorelick, M.H., Grabowski, L. & Kelly, K.J. 2006. National Asthma Education and Prevention Program severity classification as a measure of disease burden in children with acute asthma. *Pediatrics,* 117(4):71-77.

Lalloo, U.G. & Mclvor, R.A. 2006. Management of chronic asthma in adults in diverse regions of the world. *International journal of tuberculosis and lung disease*, 10(5):474-483.

Lalloo, U., Ainslie, G., Wong, M., Abdool-Gaffer, S., Irusen, E., Mash, R., Feldman, C., O'Brien, J. & Jack, C. 2007a. Guidelines for the management of chronic asthma in adolescents and adults. *The South African Pharmaceutical practice,* 49(5):19-31.

Lalloo, U., Ainslie, G., Wong, M., Abdool-Gaffer, S., Irusen, E., Mash, R., Feldman, C., O'Brien, J. & Jack, C. 2007b. Guidelines for the management of chronic asthma in adolescents and adults. *The South African Pharmaceutical practice,* 74(8):28-41.

Lalloo, U.G., Ainslie, G.M., Abdool-Gaffar, M.S., Awotedu, A.A., Feldman, C., Greenblatt, M., Irusen, E.M., Mash, R., Naidoo, S.S., O'Brien, J., Otto, W., Richards, G.A. & Wong, M.L. 2012. Guideline for the management of acute asthma in children: 2013 update. *South African medical journal,* 103(3):189-198.

Lang, J.E. 2012. Obesity, nutrition, and asthma in children. *Pediatric allergy, immunology, and pulmonology*, 25(2):64-75.

Lavoie, K.L., Bacon, S.L., Barone, S., Cartier, A., Ditto, D. & Labrecque, M. 2006. What is worse for asthma control and quality of live: depressive disorders, anxiety disorders, or both? *Chest journal,* 130(4):1039-1047.

Lazarus, S.C., Chinchilli, V.M., Rollings, N.J., Boushey, H.A., Cherniack, R., Craig, T.J., Deykin, A., DiMango, E., Fish, J.E., Ford, J.G., Israel, E., Kiley, J., Kraft, M., Lemanske, R.F., Leone, F.T., Martin, R.J., Pesola, G.R., Peters, S.P., Sorkness, C.A., Szefler, S.J., Wechsler, M.E., Fahy, J.V. & the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. 2007. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonist in asthma. *American journal of respiratory and critical care medicine,* 175(8):783-790.

Lehohla, P. 2011. *Mid-year population estimates, 2011* [Homepage of Statistics South Africa], [Online]. Available: http://www.statssa.gov.za/ Date of access: 8 February 2012.

Lencher, K.I. & Saltoun, C. 2004. Asthma classification. *Allergy and asthma proceedings,* 25(4):S21-S22.

Leynaert, B., Sunyer, J., Garcia-Esteban, R., Svanes, C., Jarvis, D., Cerveri, I., Dratva, J., Gislason, T., Heinrich, J., Janson, C., Kuenzli, N., de Marco, R., Omenaas, E., Raherison, C., Gómez Real, F., Wjst, M., Zemp, E., Zureik, M., Burney, P.G.J., Anto, J.M. & Neukirch,

F. 2012. Gender differences in prevalence, diagnoses and incidence of allergic and non-allergic asthma: a population-based cohort. *Thorax,* 67(7):625-631.

Li, C. & Hung Wong, W. 2001. Model-based analysis of oligonucleotide arrays: model validation, design issues and standard error application. *Genome biology,* 2(8):1-10.

Lindgren, A., Björk, J., Stroh, E. & Jakobsson, K. 2010. Adult asthma and traffic exposure at residential address, workplace address, and self-reported daily time outdoor traffic: a two-stage case-control study. *BMC public health,* 10(716):1-12.

Lombardo, L.J. & Balmes, J.R. 2000. Occupational asthma: a review. *Environmental health perspective,* 108(4):697-704.

Lötvall, J., Akdis, C.A., Bacharier, L.B., Bjermer, L., Casale, T.B., Custovic, A., Lemanske, R.F., Wardlaw, A.J., Wenzel, S.E. & Greenberg, P.A. 2011. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. The journal of allergy and clinical immunology*,* 127(2):355-360.

Löwhagen, O. 2012. Diagnosis of asthma: – a new approach. *Allergy journal,* 67(6):713-717.

Lu, Y., Mak, K.K., van Bever, H.P.S., Ng, T.P., Mak., A & Ho., R.C. 2012. Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. *Pediatric allergy and immunology,* 23(8):707-715.

Lyles, A., Sleath, B., Fulda, T.R., & Collins, T.M. 2001. Ambulatory drug utilization review: opportunities for improved prescription drug use. *The American journal of managed care,* 7(1):75-81.

Machado, R.B., Pereira, A.P., Coelho, G.P., Neri, L., Martins, L. & Luminoso, D. 2010. Epidemiological and clinical aspects of migraine in user of combined oral contraceptives. *Contraception,* 81(3):202-208.

MacIntyre, U.E., de Villiers, F.P.R. & Owange-Iraka, J.W. 2001. Increase in childhood asthma admissions an urbanising population. *South African medical journal,* 91(8):667-672.

Mahboub, B.H., Al-Hammadi, S., Rafique, M., Sulaiman, N., Pawankar, R., Al Redha, .A.I. & Mehta, A.C. 2012. Population prevalence of asthma and its determinants based on European Community Respiratory Health Survey in the United Arab Emirates. *BMC pulmonary medicine,* 12(4):1-8.

Maher, J.M., Markey, J.C. & Ebert-May, D. 2013. The other half of the story: effect size in quantitative research. *American Society for Cell Biology: life sciences education,* 12(3):345-351.

Mallol, J., Crane, J., von Mutius, E., Odehiambo, J., Keil, U. & Stewart, A. 2013. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. *Allergologia et immunopathologia,* 41(2):73-85.

Marcus, P. & Braman, S.S. 2010. International classification of disease coding for obstructive lung disease: does it reflect appropriate clinical documentation? *Chest journal,* 138(1):188-192.

Martinez, F.D., Wright, A.L., Taussig, L.M., Holberg, C.J., Halonen, M. & Morgan, W.J. 1995. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *The New England journal of medicine,* 332(3):133-138.

Mash, B., Rhode, H., Pather, M., Ainslie, G., Irusen, E., Bheekie, A. & Mayers, P. 2009. Quality of asthma care: Western Cape Province, South Africa. *South African medical journal,* 99(12):892-896.

Masoli, M., Fabian, D., Holt, S. & Beasley, R. 2003. Global burden of asthma. GINA. http://www.ginasthma.org/Global-Burden-of-Asthma Date of access: 15 Feb. 2012.

Masoli, M., Fabian, D., Holt, S. & Beasley, R. 2004. The global burden of asthma: executive summary of the GINA dissemination committee report. *Allergy journal,* 59(1):469-478.

McCallister, J.W., Parsons, J.P. & Mastronarde, J.G. 2011. The relationship between gastroesophageal reflux and asthma; an update. *Therapeutic advances in respiratory disease,* 5(2):143-150.

McDonald, N.J., & Bara, A.I. 2003. Anticholinergic therapy for children over two years of age. *Cochrane database of systematic reviews, 1*(3):CD003535.

Miller, R. L. & Ho, S.M. 2008. Environmental epigenetics and asthma: current concepts and call for studies. *American journal of respiratory and critical care medicine,* 177(6):567-573.

Miravitlles, M., Andreu, I., Romero, Y., Sitjar, S., Altés, A. & Anton, E. 2012. Difficulties in differential diagnoses of COPD and asthma in primary care. *The British journal of general practice,* 62(595):68-75.

Motala, C., Green, R.J., Manjra, A.I., Potter, P.C. & Zar, H.J. 2009. Guideline for the management of chronic asthma in children – 2009 update. *South African medical journal,* 99(12):898-912.

Motola, D. & De Ponti, F. 2006. Generic versus brand-name medical products: are they really interchangeable? *Digestive and liver disease,* 38(8):560-562.

Moulton, B.C. & Fryer, A. 2011. Muscarinic receptor antagonists, from folklore to pharmacology; finding drugs that actually work in asthma and COPD. *British journal of pharmacology*, 163(1):44-52.

Mouton, J. 2010. The treatment of paediatric asthma in the private health care sector of South Africa: A retrospective drug utilization review. Potchefstroom: North-West University. (Dissertation – M.Pharm). 177p.

Myers, T.R. 2008. Guidelines for asthma management: a review and comparison of 5 current guidelines. *Respiratory care,* 53(6):751-769.

Myers, T.R. & Tomasio, L. 2011. Asthma: 2015 and beyond. *Journal of respiratory care,* 56(9):1389-1407.

NAEPP (National Asthma Education and Prevention Program). 2007. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and management of asthma-summary report 2007. The journal of allergy and clinical immunology, 120(5):S94-S138.

Nagai, H. 2012. Recent research and development strategy of anti-asthma drugs. *Pharmacology and therapeutics,* 133(1):70-78.

Navarro, R.P., Schaecher, K.L. & Rice, G.K. 2007. Asthma management guidelines: updates, advances and new options. *Journal of managed care pharmacy,* 13(6):S3-S11.

Nicolaou, N., Siddique, N. & Custovic, A. 2005. Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy journal,* 60(11):1357-1360.

Nriagu, J., Robins, T., Gary, L., Liggans, G., Davila. R., Supuwood, K., Harvey, C., Jinabhai, C.C. & Naidoo, R. 1999. Prevalence of asthma and respiratory symptoms in south-central Durban, South Africa. *European journal of epidemiology,* 15(8):747-755.

O'Byrne, P.M. 2010. Global guidelines for asthma management: summary of the current status and future challenges. *Polskie Archiwum Medycyny Wewnetrznej,* 120(12):511-517.

Ober, C. & Yao, T.C. 2011. The genetics of asthma and allergic disease: a 21st century perspective. *Immunological reviews,* 242(1):10-30.

Obihara, C.C., Marais, B.J., Gie, R.P., Potter, P., Bateman, E.D., Lombard, C.J., Beyers, N. & Kimpen, J.L.L. 2005. The association of prolonged breastfeeding and allergic diseases in poor urban children. *The European respiratory journal,* 25(6):970-977.

OED: Oxford English Dictionary. 2013. Percentage. http://www.oxforddictionaries.com/ Date of access: 10 Oct. 2013.

OED: Oxford English Dictionary. 2013. Prevalence. http://www.oxforddictionaries.com/ Date of access: 10 Oct. 2013.

Opolski, M. & Wilson, I. 2005. Asthma and depression: a pragmatic review of the literature and recommendations for future research. *Clinical practice and epidemiology in mental health,* 1(18):1-7.

Pandis, N. 2013 . The *P* value problem. *American journal of orthodontics and dentofacial orthopedics*, 143(1):150-151.

Papadopoulos, N.G., Arakawa, H., Carlsen, K.H., Custovic, A., Gern, J., Lemanske, R., Le Souef, P., Mäkelä, M., Roberts, G., Wong, G., Zar, H., Akdis, C.A., Bacharier, L.B., Baraldi, E., van Bever, H.P., de Blick, J., Boner, A., Burks, W., Casale, T.B., Castro-Rodriguez, J.A., Chen, Y.Z., El-Gamal, Y.M., Everard, M.L., Frischer, T., Geller, M., Gereda, J., Goh, D.Y., Guilbert, T.W., Hedlin, G., Heyman, P.W., Hong, S.J., Hossny, E.M., Huang, J.L., Jackson, D.L., de Jongste, J.C., Kalayci, O., Aït-Khaled, N., Kling, S., Kuna, P., Lau, S., Ledford, D.K., Lee, S.I., Lui, A.H., Lockey, R.F., Lødrup-Carlsen, K., Lötvall, J., Morikawa, A., Nieto, A., Paramesh, H., Pawankar, R., Pohunek, P., Pongracic, J., Price, D., Robertson, C., Rosario, N., Rossenwasser, L.J., Sly, P.D., Stein, R., Stick, S., Szefler, S., Taussig, L.M., Valovirta,E., Vichyanond, P., Wallace, D., Weinberg, E., Wennergren, G., Wildhaber, J. & Zeiger, R.S. 2012. International consensus on (ICON) pediatric asthma. *Allergy journal,* 67(8):976-997.

Papadopoulos, N.G., Christodoulou, I., Rhode, G., Agache, I., Almqvist, C., Bruno, A., Bonini, S., Bont, L., Bossios, A., Bousquet, J., Braido, F., Brusselle, G., Canonica, G.W., Carlsen, K.H., Chanez, P., Fokkens, W.J., Garcia-Garcia, M., Gjomarkaj, M., Haahtela, T., Holgate, S.T., Johnston, S.L., Konstantinou, G., Kowalski, M., Lewandowsk-Polka, A., Lødrup-Carlsen, K., Mäkelä, M., Malkkusova, I., Mullol, J., Nieto, A., Eller, E., Ozdemir, C., Panzer, P., Popov, T., Psarras, S., Roumpedaki, E., Rukhadze, M., Stipic-Markovic, A., Todo Bom, A., Toskala, E., van Cauwenberge, P., van Drunen, C., Watelet, J.B., Xatzipsalti,

M., Xepapadaki & Zuberbier, T. 2011. Viruses and bacteria in acute asthma exacerbations – a GA^2 LEN-DARE systematic review. *Allergy journal,* 66(4):458-468.

Papiris, S., Kotanidou, A., Malagari, K. & Roussos, C. 2002. Clinical review: severe asthma. *Critical care,* 6(1):30-44.

Papiris, S.A., Effrosyni, D.M., Kolilekas, L., Triantafillidou, C. & Tsangaris, I. 2009. Acute severe asthma: new approaches to assessment and treatment. *Drugs,* 69(17):2363-2391.

Park, J.G., Ramar, K. & Olsen, E.J. 2011. Updates on definition, consequences and management of obstructive sleep apnea. *Mayo clinic proceedings,* 86(6):549-555.

Patel, A., Gauld, R., Norris, P. & Rades, T. 2012. Quality of generic medicines in South Africa: perceptions versus reality – a qualitative study. *BMC health research,* 12(297):1-10.

Pearce, N. & Douwes, J. 2005. Commentary: asthma time trends - mission accomplished? *International journal of epidemiology,* 34(5):1018-1019.

Pearce, N. & Douwes, J. 2012. Lifestyle changes and childhood asthma. *Indian journal of pediatrics,* 80(1):S95-S99.

Pearce, N., Aït-Khaled, N., Beasley, R., Mallol, J., Keil, U., Mitchell, E. & Robertson, C. 2007. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax,* 62(9):758-766.

Pearson, E.S. & Hartley, H.O. 1972. Biometrika tables for statistics 2nd volume. Cambridge: University of Cambridge. 385p.

Peden, D. & Reed, C.E. 2010. Environmental and occupational allergies. *The journal of allergy and clinical immunology,* 125(2):150-160.

Pérez-Vicente, S. & Expósito Ruiz, M. 2009. Descriptive statistics. *Allergologia et immunopathologia,* 37(6):314-320.

Peters, S.P., Kunselman, S.J., Icitovic, N., Moore, W.C., Pascual, R., Ameredes, B.T., Boushey, H.A., Calhoun, W.J., Castro, M., Cherniack, R.M., Craig, T., Denlinger, D., Engle, L.L., DiMango, E.A., Fahy, J.V., Isreal, E., Jarjour, N., Kazani, S.D., Kraft, M., Lazarus, S.C., Lemanske, R.F., Lugogo, N., Martin, R.J., Meyers, D.A., Ramsdell, J., Sorkness, C.A., Sutherland, E.R., Szefler, S.J., Wasserman, S.I., Walter, M.J., Wechsler, M.E., Chinchili, V.M. & Bleecker., E.R. 2010. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *The New England journal of medicine,* 363(18):1715-1726.

Picado, C. & Valero, A. 2001. COX-1 sparing drugs in aspirin-sensitive asthma. *Clinical and experimental allergy,* 31(2):179-181.

Pierce, R. & Irving, L. 1991. The National Asthma Campaign: – a measurable public health exercise. *Australian and New Zealand journal of medicine*, 21(1):4-5.

Platts-Mills, T.A., Erwin, E., Heymann, P. & Woodfolk, J. 2005. Is the hygiene hypotheses still a viable explanation for the increased prevalence of asthma? *Allergy journal,* 60(79):25-31.

Polosa, R. & Benfatto, G.T. 2009. Managing patients with chronic severe asthma: rise to the challenge. *European journal of internal medicine,* 20(2):114-124.

Postma, D.S. 2007. Gender differences in asthma development and progression. *Gender medicine,* 4(1):133-146.

Potter, P.C. 2010. Current guidelines for the management of asthma in young children. *Allergy, asthma & immunology research*, 2(1):1-13.

Poyser, M.A., Nelson, H., Ehrlich, R.I., Bateman, E.D., Parnell, S., Puterman, A. & Weinberg, E. 2002. Socioeconomic deprivation and asthma prevalence and severity in young adolescents. *The European respiratory journal,* 19(5):892-898.

Price, D. & Thomas, M. 2006. Breaking new ground: challenging existing asthma guidelines. *BMC pulmonary medicine*, 6(1):1-8.

Reddel, H.K., Taylor, D.R., Bateman, E.D., Boulet, L.P., Boushey, H.A., Busse, W.W., Casale, T.B., Chanez, P., Enright, P.L., Gibson, P.G. de Jongste, J.C., Kerstjens, H.A.M., Lazarus, S.C., Levy, M.L., O'Byrne, P.M., Partridge, M.R., Pavord, I.D., Sears, M.R., Sterk, P.J., Stoloff, S.W., Sullivan, S.D., Szefler, S.J., Thomas, M.D. & Wenzel S.E. 2009. An official American Thoracic Society/European Respiratory Society statement: asthma and exacerbations; standardizing endpoints for clinical asthma trails and clinical practice control. *American journal of respiratory and critical care medicine,* 180(1):59-99.

Reed, C.E. 2006. The natural history of asthma. *The journal of allergy and clinical immunology,* 118(3):543-548.

Robinson, C.L., Baumann, L.M., Romero, K. Combe, J.M., Gomez, A., Gilman, R.H., Cabrera, L., Gonzalvez, G., Hansel, N.N., Wise, R.A., Barnes, K.C., Breysse, P.N. & Checkley, W.

2011. Effect of urbanisation on asthma, allergy and airways inflammation in a developing country setting. *Thorax,* 66(12):1051-1057.

Sembajwe, G., Cifuentes, M., Tak, S.W., Kriebel, D., Gore, R. & Punnett, L. 2010. National income, self-reported wheezing and asthma diagnoses from the World Health Survey. *The European respiratory journal,* 35(2):279-286.

Serfontein, C.B. 1996. Drug utilization review: third party payer's perspective. Potchefstroom: North-West University. (Dissertation – M.Pharm). 217p.

Sheehan, W.J., Rangsithienchai, P.A., Wood, R.A., Rivard, D., Chinratanapisti, S., Perzanowski, M.S., Chew, G.L., Seltzer, J.M., Matsui, E.C. & Phipatanakul, W. 2010. Pest and allergen exposure and abatement in inner-city asthma: a work group report of the American Academy of Allergy, Asthma & Immunology Indoor Allergy/Air Pollution Committee. *The journal of allergy and clinical immunology,* 125(3):575-581.

Shin, J.W., Sue, J.H., Song, T.W., Kim, K.W., Kim, E.S., Sohn, M.H. & Kim, K.E. 2005. Atopy and house dust mite sensitization as risk factors for asthma in children. *Yonsei medical journal,* 46(5):629-634.

Skoner, D.P. 2002. Balancing safety and efficacy in pediatric asthma management. *Pediatrics,* 109(2):381-392.

Snyman, J.R., ed. 2009. Respiratory system. *Monthly index of medical specialties, 49(3):152-157*

Soumerai, S.B. & Lipton, H.L. 1995. Computer-based drug-utilization review-risk, benefit, or boondoggle. *The New England journal of medicine,* 332(24):1641-1645.

South Africa. Department of Health. 2008. Standard treatment guidelines and essential medicines list. Pretoria: Government Printer. 407p.

SSC (Statistics Solutions Consulting). 2006. Descriptive statistics. http://www.socialresearchmethods.net/kb/statdesc.php Date of access: 11 Nov. 2012.

SSC (Statistics Solutions Consulting). 2012. Nominal variable association. http://www.statisticssolutions.com/academic-solutions/resources/directory-of-statistical-analyses/nominal-variable-association/ Date of access: 12 Nov. 2013

Stanciole, A.E., Ortegón, M., Chisholm, D. & Lauer J.A. 2012. Cost effectiveness of strategies to combat chronic obstructive pulmonary disease and asthma in sub-Saharan

Africa and South East Asia: mathematical modeling study. *British medical journal,* 2(344):e608.

Sterling, Y.M. 2012. Impact of the environment on asthma control. *Journal of community health nursing,* 29(3):143-153.

Steyn, K., Bradshaw, D., Norman, R., Laubscher, R. & Saloojee, Y. 2002. Tobacco use in South Africans during 1998: the first demographic and health survey. *Journal of cardiovascular risk,* 9(3):161-170.

Subbarao, P., Mandhane, P.J. & Sears, M.R. 2009. Asthma: epidemiology, etiology and risk factors. *Canadian Medical Association journal,* 181(9):181-190.

Sullivan, P.W., Ghushschyan, V.H., Slejko, J.F., Belozeroff, V., Globe, D.R. & Lin, S.L. 2011. The burden of adult asthma in the United States: evidence from the Medical Expenditure Panel Survey. *The journal of allergy and clinical immunology,* 127(2):363-369.

Szczeklik, A. & Stevenson, D.D. 2003. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *The journal of allergy and clinical immunology,* 111(5):913-921.

Taborda-Barata, L. & Potter, P.C. 2012. Socio-epidemiological Aspects of Respiratory Allergic Diseases in Southern Africa. *The World Allergy Organization journal,* 5(1):1-8.

Takenoue, Y., Kaneko, T., Miyamae, T., Mori, M. & Yokota, S. 2012. Influence of outdoor NO_2 exposures on asthma in child hood: meta-analysis. *Pediatrics International: official journal of the Japan Pediatric Society,* 54(6):762-769.

Ten Brinke, A., Sterk, P.J., Masclee, A.A.M., Spinhoven, P., Schimdt, J.T., Zwinderman, A.H., Rabe, K.F. & Bel, E.H. 2005. Risk factors of frequent exacerbations in difficult-to-treat asthma. The *European respiratory journal,* 26(5):812-818.

Thomsen, S.F., Duffy, D.L., Kyvik, K.O. & Backer, V. 2010. Genetic influence on the age onset of asthma: a twin study. *The journal of allergy and clinical immunology,* 126(3):626-630.

To, T., Stanojevic, S., Moores, G., Gershon, A.S., Bateman, E.D., Cruz, A.A. & Boulet, L.P. 2012. Global asthma prevalence in adults: findings from cross-sectional world health survey. *BMC public health*, 12(204):1-8.

Tomlins, R. 2006. International Primary Care Respiratory Group (IPCRG) Guidelines: Dissemination and implementation: – a proposed course of action. *Primary care respiratory journal,* 15(1):71-74.

Tsai, C.L., Lee, W.Y., Hanania, N.A. & Camargo, C.A. 2012. Age-related differences in clinical outcomes for acute asthma in the United States, 2006-2008. *The journal of allergy and clinical immunology,* 129(5):1252-1258.

Tse, S.M., Tantisira, K. & Weiss, S.T. 2011. The pharmacogenetics and pharmacogenomics of asthma therapy. *The pharmacogenomics journal,* 11(6):383-392.

Urbano, F.L. 2008. Review of the NAEPP 2007 Expert Panel Report (EPR-3) on Asthma Diagnosis and Treatment Guidelines. *Journal of managed care pharmacy,* 14(1):41-49.

Van den Berge, M., Heijink, H.I., van Oosterhout, A.J.M. & Postma, D.S. 2009. The role of female sex hormones in the development and severity of allergic and non-allergic asthma. *Clinical & experimental allergy,* 39(10):1477-1481.

Van der Molen, T., Østerm, A., Stallberg, B., Østergaard, M.S. & Singh, R.B. 2006. International primary Care Respiratory Group (IPCRG) Guidelines: management of asthma. *Primary care respiratory journal,* 15(1):35-47.

Van Ganse, E., Antonicelli, L., Zhang, Q., Laforest, L., Yin, D.D., Nocea, G. & Sazonov Kocevar, V. 2006. Asthma-related resource use and cost by GINA classification on severity in three European countries. *Respiratory medicine,* 100(1):140-147.

Van Gemert, F., Van der Molen, T., Jones, R, & Chavannes, N. 2011. The impact of asthma and COPD in sub-Saharan Africa. *Primary care respiratory journal,* 20(3):240-248.

Van Walbeek, C., Blecher, E. & van Graan, M. 2007. Effects of the Tobacco Products Amendment act of 1999 on restaurant revenues in South Africa – a survey approach. *South African medical journal,* 97(3):208-211.

Van Weel, C., Bateman, E.D., Bousquet, J., Reid, J., Grouse, L., Schermer, T., Valovirta, E. & Zhong, N. 2008. Asthma management pocket reference 2008. *Allergy journal,* 63(8):997-1004.

Vane, J.R. & Botting, R.M. 2003. The mechanism of action of aspirin. *Thrombosis research,* 110(5-6):255-258.

Vane, J.R. & Warner, T.D. 2000. Nomenclature for COX-2 inhibitors. *Lancet,* 356(9239):1373-1374.

Vianna, E.O., Garcia, C.A., Bettiol, H., Barbieri, M.A. & Rona, R.J. 2007. Asthma definitions, relative validity and impact on known risk factors in young Brazilians. *Allergy journal,* 62(10):1146-1151.

Vink, N.M., Postma, D.S., Schouten, J.P. Rosmalen, J.G.M. & Boezen, H.M. 2010. Gender differences in asthma development and remission during transition through puberty: the Tracking Adolescents' Individual Lives Survey (TRAILS) study. The journal of allergy and clinical immunology*,* 126(3):498-504.

Volkman, J.A. & Pontikes, P.J. 2002. Leukotriene modifiers to prevent aspirin-provoked respiratory reactions in asthmatics. *The Annals of pharmacotherapy,* 36(9):1457-1461.

Walters, J.A.E., Wood-Baker, R. & Walters, E.H. 2005. Long–acting β_2–agonists in asthma: an overview of Cochrane systematic reviews. *Respiratory medicine,* 99(4):384-395.

Weinberger, M. 2004. Managing asthma: past, present and future. *The journal of pediatric pharmacology and therapeutics,* 9(1):6-14.

Weinberger, M. & Hendeles, L. 1996. Theophylline in asthma. *The New England journal of medicine,* 334(21):1380-1388.

Weiss, S.T., Litonjua, A.A., Lange, C., Lazarus, R., Liggett, S.B., Bleecker, E.R. & Tantisira, K.G. 2006. Overview of the pharmacogenetics of asthma treatment. *The pharmacogenomics journal,* 6(5):311-326.

Whitley, E. & Ball, J. 2002. Statistics review 1: presenting and summarising data. *Critical Care,* 6(1):66-71.

WHO (World Health Organization). 2008a. Global alliance against respiratory disease: Action plan 2008-2013. http://www.who.int/gard/publications/action_plan/en/ Date of access: 3 Jun. 2013.

WHO (World Health Organization). 2008b. COPD predicted to be the third leading cause of death in 2030. http://www.who.int/respiratory/copd/World_Health_Statistics_2008/en/ Date of access: 3 Jun. 2013.

WHO (World Health Organization). 2012. Depression. http://www.who.int/mental_health/management/depression/en/ Date of access: 6 Jun. 2013.

WHO (World Health Organization). 2013a. Bronchial asthma. http://www.who.int/mediacentre/factsheets/fs206/en/ Date of access: 13 May 2013.

WHO (World Health Organization). 2013b. Asthma: Definition http://www.who.int/respiratory/asthma/definition/en/ Date of access: 29 May 2013.

Wicht, C.L., de Kock, M.A. & van Wyk Kotze, T.J. 1977. An epidemiological study of the diffuse obstructive pulmonary syndrome. *South African medical journal,* 52(27):1-15.

Wildhaber, J., Carroll, D.W. & Brand, P.L.P. 2012. Global impact of asthma on children and adolescents' daily lives: the room to breathe survey. *Pediatric pulmonology,* 47(4):346-357.

Wjst, M. & Boakye, D. 2007. Asthma in Africa. *Plos medicine,* 4(2):203-205.

Woolcock, A., Rubinfield, A.R., Seale, J.P., Landau, L.L., Antic, R., Mitchell, C., Rea, H.H. & Zimmerman, P. 1989. Thoracic society of Australia and New Zealand. Asthma Management plan, 1989. *The Medical journal of Australia*, 151(11-12):650-653.

Yawn, B.P., van der Molen, T. & Humbert, M. 2005. Asthma management: are GINA guidelines appropriate for daily clinical practice? *Primary care respiratory journal,* 14(6):294-302.

Yigla, T., Tov, N., Solomonov, A., Rubin, A.H. & Harlev, D. 2003. Difficult-to-control asthma and obstructive sleep apnea. *The journal of asthma,* 40(8):865-871.

Yorgancioğlu, A. & Sakar Coskun, A. 2012. Is the diagnosis of asthma different in elderly? *Tüberküloz ve toraks,* 60(1):81-85.

Zar, H.J. & Lalloo, U.G. 2013. Acute asthma treatment guidelines: Reducing morbidity and mortality in South Africa. *South African medical journal,* 103(3):159-160.

APPENDIX A

SINGLE PRODUCTS:

Table A1: The top 10 observations with single active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 39 254			2008 Products	Asthma & COPD = 13 258		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone	10 555	312.30 ± 69.03	3 296 276.9	**1. Theophylline**	4 241	111.10 ± 52.09	471 167.85
2. Salbutamol	4 569	37.33 ± 23.96	1 70 543.57	**2. Fluticasone**	2 069	336.38 ± 72.89	695 978.62
3. Budesonide/ Formoterol	4 331	319.15 ± 79.89	1 382 254.09	**3. Fenoterol / Ipratropium**	1 381	181.93 ± 67.57	251 245.53
4. Theophylline	2 799	104.09 ± 59.00	2 91 350.03	**4. Salbutamol**	1 251	35.99 ± 25.80	45 018.12
5. Prednisone	2 788	32.14 ± 54.63	89 610.88	**5. Budesonide/ Formoterol**	1 078	336.75 ± 88.44	363 020.87
6. Montelukast	2 610	308.76 ± 68.88	805 872.33	**6. Ipratropium/ Salbutamol**	859	179.58 ± 131.82	154 255.66
7. Budesonide	2 566	209.28 ± 68.99	537 023.98	**7. Formoterol**	649	172.50 ± 77.50	111 957.43
8. Beclomethasone	1 120	163.78 ± 53.27	183 443.77	**8. Salbutamol/ Ipratropium**	576	260.08 ± 152.59	149 806.09
9. Formoterol	861	197.61 ± 78.14	140 146.27	**9. Bromhexine/ Orciprenaline**	369	34.95 ± 17.89	12 895.25
10. Bromhexine/ Orciprenaline	830	30.07 ± 13.88	24 959.33	**10. Salmeterol**	350	276.37 ± 15.83	96 729.89

Table A2: The top 10 observations with single active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 56 647			2009 Products	Asthma & COPD = 18 117		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone	13 798	351.48 ± 73.81	4 849 742.96	**1. Theophylline**	4 795	114.77 ± 60.01	550 315.07
2. Salbutamol	9 094	35.07 ± 23.50	318 949.07	**2. Tiotropium**	3 156	520.01 ± 278.21	1 641 167.68
3. Budesonide/ Formoterol	7 562	355.12 ± 91.81	2 685 450.84	**3. Fluticasone**	2 457	373.07 ± 80.50	916 640.86
4. Theophylline	4 540	99.09 ± 58.91	449 847.58	**4. Budesonide/ Formoterol**	1 631	374.60 ± 104.08	610 966.58
5. Montelukast	4 234	337.93 ± 86.63	1 430 778.2	**5. Fenoterol/ Ipratropium**	1 368	201.89 ± 61.74	276 183.24
6. Prednisone	4 105	30.89 ± 52.90	126 790.02	**6. Salbutamol**	1 235	42.67 ± 50.08	526 183.24
7. Formoterol	2 693	164.67 ± 80.52	443 480.50	**7. Ipratropium/ Salbutamol**	950	190.86 ± 135.78	181 316.28
8. Fenoterol/ Ipratropium	1 674	194.97 ± 82.61	321 114.93	**8. Salbutamol/ Ipratropium**	786	262.96 ± 174.20	206 683.22
9. Salmeterol	1 539	296.80 ± 31.04	456 785.16	**9. Formoterol**	753	177.05 ± 97.01	133 322.55
10. Betamethasone	1 196	72.50 ± 59.29	86 707.46	**10. Salmeterol**	390	305.62 ± 28.12	119 190.27

Table A3: The top 10 observations with single active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 51 839			2010 Products	Asthma & COPD = 16 191		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone	11 458	371.68 ± 81.60	4 258 697.96	**1. Theophylline**	4 542	122.53 ± 61.36	556 545.02
2. Salbutamol	7 745	34.59 ± 20.22	267 937.59	**2. Fluticasone**	2 186	389.85 ± 99.93	852 216.40
3. Budesonide/ Formoterol	7612	372.36 ± 102.23	2 834 427.66	**3. Tiotropium**	2 034	528.51 ± 122.32	1 074 995.88
4. Montelukast	4 326	349.38 ± 97.33	1 511 407.30	**4. Budesonide/ Formoterol**	1 665	383.75 ± 102.68	638 950.02
5. Theophylline	4 119	104.23 ± 61.69	429 321.19	**5. Salbutamol**	1 133	41.27 ± 45.78	46 755.83
6. Prednisone	3 683	30.56 ± 54.27	112 591.86	**6. Fenoterol/ Ipratropium**	1 071	215.90 ± 73.58	231 227.25
7. Formoterol	2 967	162.40 ± 78.27	481 861.44	**7. Salbutamol/ Ipratropium**	862	255.43 ± 166.99	220 184.38
8. Salmeterol	1 560	308.04 ± 47.28	480 539.59	**8. Formoterol**	807	164.76 ± 88.36	132 957.52
9. Fenoterol/ Ipratropium	1 261	199.86 ± 88.77	252 022.93	**9. Formoterol**	769	198.57 ± 151.99	152 697.47
10. Betamethasone	1 059	75.50 ± 69.93	79 946.09	**10. Salmeterol**	414	319.55 ± 50.64	132 291.74

Table A4: The top 10 observations with single active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 29 979			2011 Products	Asthma & COPD = 12 601		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Budesonide/ Formoterol	5 707	378.61 ± 94.50	2 160 780.85	**1. Theophylline**	4 106	116.92 ± 60.18	480 098.54
2. Salmeterol/ Fluticasone	5 314	289.17± 50.20	1 536 635.16	**2. Salmeterol/ Fluticasone**	1 754	307.00 ± 52.50	538 485.89
3. Fluticasone	3 910	347.95 ± 104.06	1 360 493.09	**3. Budesonide/ Formoterol**	1 490	395.37 ± 109.12	589 101.56
4. Budesonide	3 040	229.16 ± 67.10	696 658.66	**4. Fenoterol/ Ipratropium**	1 027	216.35 ± 65.43	222 193.07
5. Salbutamol	2 888	37.77 ± 40.60	109 070.43	**5. Salbutamol**	1 019	37.55 ± 33.52	38 262.25
6. Montelukast	1 962	375.73 ± 40.13	737 179.97	**6. Fluticasone**	761	386.58 ± 79.18	294 191.01
7. Theophylline	1 939	100.34 ± 58.79	194 563.96	**7. Tiotropium**	705	534.85 ± 142.76	377 076.08
8. Beclomethasone	1 272	185.63 ± 49.10	236 125.74	**8. Formoterol**	595	167.17 ± 85.263	99 469.46
9. Salmeterol	1 150	272.29 ± 51.64	313 132.98	**9. Salbutamol/ Ipratropium**	466	177.87 ± 64.84	82 891.59
10. Formoterol	752	167.76 ± 80.94	126 155.94	**10. Salmeterol**	450	350.53 ± 39.64	137 491.08

TWO PRODUCTS

Table A5: The top 10 observations with two active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 19 085			2008 Products	Asthma & COPD = 4 361		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Salbutamol	1 490	356.564 ± 78.11	531 281.36	**1. Fenoterol/ Ipratropium, Theophylline**	490	305.25 ± 110.81	149 577.3
2. Salbutamol, Budesonide	1 364	232.24 ± 53.04	316 784.02	**2. Fluticasone, Theophylline**	379	484.09 ± 83.80	183 471.94
3. Fluticasone, Montelukast	1 017	617.19 ± 111.92	627 691.13	**3. Theophylline, Salbutamol**	343	145.75 ± 73.80	49 992.61
4. Budesonide, Salbutamol	873	247.33 ± 78.75	215 927.48	**4. Salbutamol, Theophylline**	277	120.66 ± 58.79	33 425.25
5. Salbutamol, Fluticasone	831	347.70 ± 74.46	288 944.45	**5. Theophylline, Fluticasone**	207	414.98 ± 84.95	85 901.6
6. Salbutamol, Beclomethasone	788	182.38 ± 44.89	143 721.91	**6. Ipratropium/ Salbutamol, Theophylline**	195	294.94 ± 115.93	57 515.15
7. Budesonide, Formoterol	529	307.76 ± 137.92	162 808.53	**7. Fenoterol/ Ipratropium, Fluticasone**	189	541.26 ± 105.15	102 299.77
8. Beclomethasone, Salbutamol	500	183.26 ± 54.20	91 634.18	**8. Budesonide/ Formoterol, Theophylline**	187	466.50 ± 133.89	87 235.62
9. Salbutamol, Budesonide/ Formoterol	405	347.22 ± 76.98	140 627.51	**9. Formoterol, Theophylline**	175	278.85 ± 115.23	48 799.08
10. Fluticasone, Theophylline	400	463.18 ± 90.27	185 272.04	**10. Fluticasone, Salbutamol**	164	376.25 ± 81.94	61 705.08

Table A6: The top 10 observations with two active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 18 380			2009 Products	Asthma & COPD = 7 202		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Montelukast	1 900	697.57 ± 153.53	1 325 392.39	**1. Fluticasone, Tiotropium**	813	880.63 ± 126.42	715 957.66
2. Fluticasone, Salbutamol	1 674	402.13 ± 75.19	673 170.09	**2. Fenoterol/ Ipratropium, Theophylline**	463	321.67 ± 105.94	148 936.6
3. Salbutamol, Fluticasone	820	389.79 ± 72.59	319 627.95	**3. Tiotropium, Budesonide/ Formoterol**	431	889.23 ± 159.93	383 258.62
4. Theophylline, Salbutamol	628	147.00 ± 76.07	92 316.57	**4. Tiotropium, Theophylline**	414	669.78 ± 86.86	277 289.68
5. Montelukast, Budesonide/ Formoterol	616	716.35 ± 152.77	441 275.82	**5. Fluticasone, Theophylline,**	354	515.54 ± 124.30	182 502.56
6. Budesonide/ Formoterol, Salbutamol	510	395.68 ± 111.25	201 800.51	**6. Theophylline, Fluticasone**	292	467.89 ± 108.38	136 625.73
7. Fluticasone, Theophylline	476	534.12 ± 100.20	254 244.87	**7. Theophylline, Salbutamol**	287	171.24 ± 150.46	49 147.66
8. Salbutamol, Budesonide/ Formoterol	448	404.57 ± 89.53	181 248.26	**8. Fenoterol/ Ipratropium, Fluticasone**	276	572.18 ± 112.27	157 921.81
9. Theophylline, Fluticasone	434	454.47 ± 97.97	197 243.95	**9. Budesonide/ Formoterol, Theophylline**	228	511.62 ± 121.77	116 649.82
10. Formoterol, Theophylline	396	220.84 ± 87.50	87 456.11	**10. Theophylline, Tiotropium**	213	561.34 ± 136.52	119 566.74

Table A7: The top 10 observations with two active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 16646			2010 Products	Asthma & COPD = 6466		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Montelukast	1 687	729.63 ± 140.06	1 230 897.06	**1. Fluticasone, Tiotropium**	543	906.50 ± 129.51	492 229.62
2. Fluticasone, Salbutamol	1 396	416.45 ± 88.75	581 368.4	**2. Fenoterol/ Ipratropium, Theophylline**	461	327.57 ± 95.82	151 011.09
3. Montelukast, Budesonide/ Formoterol	813	754.05 ± 151.61	613 045.57	**3. Fluticasone, Theophylline**	410	548.99 ± 109.54	225 085.9
4. Salbutamol, Fluticasone	684	402.19 ± 75.04	275 101.6	**4. Tiotropium, Budesonide/ Formoterol**	347	913.74 ± 197.34	317 068.36
5. Theophylline, Salbutamol	643	143.27 ± 68.09	92 124.42	**5. Theophylline, Fluticasone,**	266	487.70 ± 89.55	129 728.21
6. Budesonide/ Formoterol, Salbutamol	491	432.24 ± 138.22	212 230.1	**6. Tiotropium, Theophylline**	262	695.58 ± 88.77	182 244.45
7. Salbutamol, Budesonide/ Formoterol	422	409.38 ± 101.51	172 760.72	**7. Fenoterol/ Ipratropium, Fluticasone**	250	595.60 ± 100.21	148 900.97
8. Salbutamol, Theophylline	417	115.75 ± 57.99	48 267.89	**8. Theophylline, Salbutamol**	238	182.01 ± 153.59	43 319.34
9. Fluticasone, Theophylline	394	577.57 ± 100.29	227 564.11	**9. Budesonide/ Formoterol, Theophylline**	236	551.17 ± 160.53	130 078.11
10. Salbutamol, Formoterol	335	151.44 ± 33.00	50 733.52	**10. Formoterol, Theophylline**	231	247.88 ± 86.09	57 262.07

Table A8: The top 10 observations with two active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 11 095			2011 Products	Asthma & COPD = 4 106		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Salbutamol, Budesonide	793	266.41 ± 60.47	211 270.53	**1. Salmeterol/ Fluticasone, Theophylline**	490	428.44 ± 64.40	209 939.32
2. Budesonide, Formoterol	662	286.05 ± 135.94	189 368.73	**2. Fenoterol/ Ipratropium, Theophylline**	419	318.01 ± 85.05	133 246.34
3. Budesonide, Salbutamol	575	277.40 ± 51.30	159 505.87	**3. Theophylline, Budesonide/ Formoterol**	238	450.79 ± 106.50	107 288.39
4. Fluticasone, Salbutamol	502	371.09 ± 107.71	186 290.33	**4. Theophylline, Salbutamol**	216	159.83 ± 133.56	34 523.86
5. Montelukast, Budesonide/ Formoterol	475	788.60 ± 134.92	374 585.54	**5. Ipratropium/ Salbutamol, Theophylline**	190	335.90 ± 207.94	63 821.88
6. Salmeterol/ Fluticasone, Salbutamol	464	342.84 ± 56.25	159 080.42	**6. Salbutamol, Theophylline**	180	132.99 ± 55.40	23 938.67
7. Salbutamol, Beclomethasone	378	217.99 ± 52.40	82 400.58	**7. Formoterol, Theophylline**	163	253.97 ± 87.70	41 398.15
8. Beclomethasone, Salbutamol	354	207.40 ± 47.89	73 419.94	**8. Fenoterol/ Ipratropium, Budesonide/ Formoterol**	139	629.39 ± 117.16	87 486.31
9. Salmeterol/ Fluticasone, Montelukast	332	659.81 ± 64.92	219 057.50	**9. Budesonide/ Formoterol, Theophylline**	126	556.20 ± 142.83	70 082.44
10. Salbutamol, Salmeterol/ Fluticasone	314	324.57 ± 43.06	101 916.13	**10. Fenoterol/ Ipratropium, Salmeterol/ Fluticasone**	115	510.73 ± 73.11	58 735.01

THREE PRODUCTS:

Table A9: The top 10 observations with three active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 5 955			2008 Products	Asthma & COPD = 1 403		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Montelukast, Salbutamol	325	674.834 ± 102.16	219 321.35	1. Fenoterol/ Ipratropium, Fluticasone, Theophylline	99	635.47 ± 145.35	62 912.48
2. Salbutamol, Budesonide, Theophylline	233	322.31 ± 76.62	75 099.19	2. Salbutamol, Formoterol, Theophylline	59	220.31 ± 56.13	12 998.6
3. Salbutamol, Beclomethasone, Theophylline	150	252.04 ± 50.11	37 807.29	3. Budesonide/ Formoterol, Theophylline, Salbutamol	57	587.86 ± 166.66	33 508.25
4. Budesonide, Theophylline, Salbutamol	119	338.98 ± 67.13	40 339.34	4. Fenoterol/ Ipratropium, Theophylline, Fluticasone	56	630.26 ± 124.35	35 294.80
5. Salbutamol, Fluticasone, Theophylline	106	498.59 ± 108.87	52 850.54	5. Fluticasone, Theophylline, Salbutamol	48	605.48 ± 149.22	29 063.18
6. Salbutamol, Theophylline, Fluticasone	103	438.98 ± 74.51	45 215.46	6. Theophylline, Fluticasone, Salbutamol	48	530.46 ± 158.73	25 462.36
7. Fluticasone, Theophylline, Salbutamol	89	481.58 ± 184.53	42 861.14	7. Fenoterol/ Ipratropium, Formoterol, Theophylline	47	402.72 ± 119.76	18 927.92
8. Salbutamol, Fluticasone, Montelukast	88	676.64 ± 76.58	59 544.66	8. Salbutamol, Theophylline, Fluticasone	41	457.66 ± 52.27	18 764.33
9. Fenoterol/ Ipratropium, Fluticasone, Theophylline	86	680.70 ± 59.48	58 540.51	9. Fenoterol/ Ipratropium, Budesonide/ Formoterol, Fluticasone	40	638.96 ± 121.54	25 558.45
10. Fenoterol/ Ipratropium, Theophylline, Fluticasone	85	610.96 ± 114.21	51 932.17	10. Fenoterol/ Ipratropium, Theophylline, Budesonide/ Formoterol	34	522.85 ± 100.98	17 777.06

Table A10: The top 10 observations with three active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 4 218			2009 Products	Asthma & COPD = 2 813		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Montelukast, Salbutamol	358	747.53 ± 112.25	267 618.83	1. Fluticasone, Tiotropium, Theophylline	231	1074.20 ± 215.32	248 141.79
2. Salbutamol, Fluticasone, Montelukast	161	738.99 ± 113.79	118 977.46	2. Theophylline, Fluticasone, Tiotropium	183	928.42 ± 192.15	169 900.89
3. Fluticasone, Montelukast, Theophylline	96	867.44 ± 177.18	83 274.52	3. Theophylline, Fluticasone, Tiotropium	150	716.85 ± 141.85	107 527.88
4. Fluticasone, Theophylline, Montelukast	79	551.76 ± 120.58	43 589.2	4. Fenoterol/ Ipratropium, Fluticasone, Theophylline	144	1018.10 ± 197.55	146 607.55
5. Formoterol, Theophylline, Salbutamol	77	273.29 ± 107.98	21 043.88	5. Tiotropium, Budesonide/ Formoterol, Theophylline	135	961.10 ± 127.22	129 749.03
6. Fenoterol/ Ipratropium, Fluticasone, Montelukast	66	942.13 ± 190.99	62 181.18	6. Theophylline, Tiotropium, Budesonide/ Formoterol	116	663.51 ± 83.49	76 967.44
7. Fenoterol/ Ipratropium, Theophylline, Fluticasone	64	622.74 ± 136.19	39 855.56	7. Fenoterol/ Ipratropium, Theophylline, Fluticasone	85	685.36 ± 186.03	58 256.15
8. Fenoterol/ Ipratropium, Fluticasone, Theophylline	57	732.24 ± 45.72	41 737.84	8. Fenoterol/ Ipratropium, Theophylline, Budesonide/ Formoterol	77	927.81 ± 152.12	71 442.10
9. Ipratropium/ Salbutamol Fluticasone, Montelukast	53	883.08 ± 131.33	46 803.41	9. Tiotropium, Budesonide/ Formoterol, Salbutamol	69	698.68 ± 149.13	48 209.51
10. Theophylline, Fluticasone, Salbutamol	53	600.10 ± 97.38	31 805.64	10. Fenoterol/ Ipratropium, Budesonide/ Formoterol, Theophylline	59	966.15 ± 81.33	57 003.26

Table A11: The top 10 observations with three active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 3 921			2010 Products	Asthma & COPD = 2 533		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Montelukast, Salbutamol	314	778.50 ± 131.96	244 449.45	**1. Fluticasone, Tiotropium, Theophylline**	220	1118.57 ± 163.03	246 086.86
2. Salbutamol, Fluticasone, Montelukast	131	725.66 ± 97.07	95 062.56	**2. Fenoterol/ Ipratropium, Fluticasone, Theophylline**	128	690.39 ± 182.14	88 370.07
3. Fluticasone, Montelukast, Theophylline	88	916.99 ± 118.28	80 695.27	**3. Theophylline, Tiotropium, Budesonide/ Formoterol**	108	1024.49 ± 188.41	110 645.77
4. Fenoterol/ Ipratropium, Fluticasone, Theophylline	86	967.30 ± 114.33	83 188.57	**4. Theophylline, Fluticasone Theophylline,**	92	944.43 ± 120.71	86 887.68
5. Formoterol, Theophylline, Salbutamol	77	310.44 ± 130.25	23 904.12	**5. Tiotropium, Budesonide/ Formoterol, Theophylline**	87	1095.71 ± 131.98	95 327.07
6. Montelukast, Budesonide/ Formoterol, Theophylline	72	942.66 ± 107.22	67 872.14	**6. Fenoterol/ Ipratropium, Theophylline, Fluticasone**	83	703.38 ± 118.07	58 380.61
7. Fenoterol/ Ipratropium, Fluticasone, Theophylline	71	779.47 ± 82.25	55 342.84	**7. Fluticasone, Tiotropium, Salbutamol**	63	979.25 ± 101.13	61 693.11
8. Salbutamol, Formoterol, Theophylline	61	225.78 ± 49.04	13 772.68	**8. Formoterol, Theophylline, Salbutamol**	58	262.78 ± 62.19	15 241.73
9. Salbutamol, Montelukast, Budesonide/ Formoterol	60	820.63 ± 89.81	49 238.14	**9. Salbutamol, Theophylline, Fluticasone**	54	519.19 ± 89.13	28 036.58
10. Salbutamol, Theophylline, Fluticasone	60	473.96 ± 161.28	28 437.88	**10. Fenoterol/ Ipratropium, Budesonide/ Formoterol, Theophylline**	53	756.25 ± 78.30	40 081.37

Table A12: The top 10 observations with three active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 2 567			2011 Products	Asthma & COPD = 1 115		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Salbutamol, Budesonide, Formoterol	112	343.52 ± 160.64	38 474.31	1. Fenoterol/ Ipratropium, Salmeterol/ Fluticasone, Theophylline	104	656.55 ± 98.71	68 281.35
2. Budesonide, Theophylline, Salbutamol	86	362.99 ± 84.15	31 217.36	2. Salbutamol, Formoterol, Theophylline	61	221.08 ± 37.60	13 486.38
3. Fenoterol, Budesonide, Theophylline	84	441.78 ± 94.94	37 109.81	3. Salmeterol/ Fluticasone, Theophylline, Salbutamol	50	518.28 ± 157.97	25 914.39
4. Salbutamol, Budesonide, Formoterol	79	354.72 ± 102.38	28 022.98	4. Fluticasone, Tiotropium, Theophylline	48	1067.27 ± 198.74	51 228.96
5. Salmeterol/ Fluticasone, Montelukast, Salbutamol	73	690.87 ± 125.66	50 434.13	5. Salbutamol, Salmeterol/ Fluticasone, Theophylline	43	478.36 ± 64.60	20 569.69
6. Budesonide, Formoterol, Salbutamol	70	346.03 ± 139.28	24 222.6	6. Fenoterol/ Ipratropium, Budesonide/ Formoterol, Theophylline	42	849.70 ± 283.98	35 687.51
7. Beclomethasone, Theophylline, Salbutamol	67	317.92 ± 42.04	21 300.89	7. Theophylline, Budesonide/ Formoterol, Salbutamol	40	512.30 ± 122.28	20 492.34
8. Fluticasone, Montelukast, Salbutamol	63	740.34 ± 108.13	46 641.55	8. Salbutamol, Budesonide/ Formoterol, Theophylline	37	646.14 ± 59.51	23 907.5
9. Budesonide, Formoterol, Theophylline	59	474.69 ± 52.10	28 006.71	9. Fenoterol/ Ipratropium, Formoterol, Theophylline	32	378.12 ± 58.97	12 099.86
10. Budesonide, Salmeterol, Salbutamol	47	646.80 ± 89.78	30 399.77	10. Budesonide/ Formoterol, Theophylline, Salbutamol	28	634.18 ± 137.01	17 757.15

FOUR PRODUCTS:

Table A13: The top 10 observations with four active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 1 271			2008 Products	Asthma & COPD = 177		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Montelukast, Theophylline, Salbutamol	23	891.64 ± 65.30	20 507.81	1. Salbutamol/ Ipratropium, Fenoterol/ Ipratropium, Theophylline, Fluticasone	17	940.20 ± 121.05	15 983.51
2. Salbutamol, Budesonide, Formoterol, Salbutamol	21	393.58 ± 98.90	8 265.28	2. Fenoterol/ Ipratropium, Salbutamol, Formoterol, Theophylline	14	499.93 ± 23.52	6 999.10
3. Salbutamol, Budesonide, Prednisone, Theophylline	21	305.73 ± 179.74	6 420.52	3. Fenoterol/ Ipratropium, Fenoterol/ Ipratropium, Theophylline, Fluticasone	13	895.84 ± 72.67	11 646.03
4. Theophylline, Fluticasone, Montelukast, Salbutamol	16	776.25 ± 66.57	12 420.01	4. Fenoterol/ Ipratropium, Formoterol, Fluticasone, Theophylline	10	991.91 ± 147.70	9 919.13
5. Fenoterol/ Ipratropium, Salbutamol, Fluticasone, Montelukast	14	1042.92 ± 26.37	14 600.96	5. Ipratropium/ Salbutamol, Budesonide/ Formoterol, Theophylline, Salbutamol	10	977.86 ± 70.91	9 778.65
6. Montelukast, Budesonide/ Formoterol, Theophylline, Salbutamol	14	850.62 ± 117.70	11 908.81	6. Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Theophylline, Salbutamol	10	754.04 ± 25.76	7 540.47
7. Prednisone, Fluticasone, Theophylline, Salbutamol	14	527.49 ± 46.96	7 384.87	7. Fenoterol, Fenoterol/ Ipratropium, Fluticasone, Theophylline	9	861.75 ± 66.44	7 755.78
8. Salbutamol, Beclomethasone, Ipratropium, Theophylline	13	415.14 ± 35.25	5 396.82	8. Salbutamol, Formoterol, Theophylline, Salbutamol	8	424.81 ± 182.21	3 398.54
9. Salbutamol/ Ipratropium, Fluticasone, Theophylline, Salbutamol	13	905.75 ± 17.21	11 774.87	9. Fenoterol/ Ipratropium, Salmeterol, Theophylline, Salbutamol	7	532.21 ± 210.67	3 725.48
10. Budesonide, Formoterol, Theophylline, Salbutamol	12	446.54 ± 00.00	5 358.48	10. Salbutamol, Fenoterol/ Ipratropium, Formoterol, Theophylline	7	418.27 ± 136.37	2 927.90

Table A14: The top 10 observations with four active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 884			2009 Products	Asthma & COPD = 809		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Theophylline, Montelukast, Budesonide/ Formoterol, Salbutamol	31	786.95 ± 65.95	24 395.47	1. Theophylline, Fluticasone, Tiotropium, Salbutamol	66	1067.11 ± 177.80	70 429.51
2. Fenoterol, Fluticasone, Montelukast, Theophylline	20	1128.71 ± 23.60	22 574.26	2. Tiotropium, Budesonide/ Formoterol, Theophylline, Salbutamol	60	1108.62 ± 93.21	66 517.35
3. Fluticasone, Montelukast, Theophylline, Salbutamol	20	1003.39 ± 52.70	20 067.9	3. Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	59	1250.75 ± 79.14	73 794.26
4. Montelukast, Budesonide/ Formoterol, Theophylline, Salbutamol	18	970.38 ± 21.12	17 466.89	4. Salbutamol, Theophylline, Fluticasone, Tiotropium	38	1088.26 ± 91.38	41 353.98
5. Fenoterol/ Ipratropium, Fluticasone, Budesonide/ Formoterol, Theophylline	15	1203.76 ± 87.93	18 056.44	5. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium	36	1198.48 ± 83.76	43 145.57
6. Prednisone, Montelukast, Budesonide/ Formoterol, Theophylline	15	949.53 ± 79.18	14 243.01	6. Fenoterol/ Ipratropium, Tiotropium, Budesonide/ Formoterol, Theophylline	27	1234.61 ± 123.40	33 334.64
7. Theophylline, Fluticasone, Montelukast, Salbutamol	15	890.50 ± 45.71	13 357.54	7. Theophylline, Tiotropium, Budesonide/ Formoterol, Salbutamol	26	1053.24 ± 135.30	27 384.38
8. Ipratropium, Fluticasone, Theophylline, Salbutamol	14	630.96 ± 21.39	8 833.57	8. Formoterol, Tiotropium, Theophylline, Salbutamol	24	985.94 ± 270.60	23 662.74
9. Prednisone, Theophylline, Fluticasone, Salbutamol	14	607.97 ± 154.11	8 511.71	9. Salbutamol/ Ipratropium, Fenoterol/ Ipratropium, Theophylline, Fluticasone	20	1134.79 ± 68.89	22 695.91
10. Salbutamol, Prednisone, Theophylline, Fluticasone	13	383.72 ± 18.92	4 988.38	10. Fenoterol, Theophylline, Fluticasone, Tiotropium	19	1143.05 ± 52.20	21 718.11

Table A15: The top 10 observations with four active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 776			2010Pproducts	Asthma & COPD = 596		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Montelukast, Theophylline, Salbutamol	36	1027.94 ± 95.70	37 005.99	1. Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	48	1317.65 ± 154.17	6 3247.44
2. Fenoterol, Fluticasone, Montelukast, Theophylline	20	1178.41 ± 32.83	23 568.24	2. Tiotropium, Budesonide/ Formoterol, Theophylline, Salbutamol	41	1159.20 ± 47.68	4 7527.33
3. Montelukast, Budesonide/ Formoterol, Theophylline, Salbutamol	16	991.72 ± 168.59	15 867.61	3. Salbutamol/ Ipratropium, Fenoterol/ Ipratropium, Theophylline, Fluticasone	25	1253.52 ± 185.26	3 1338.23
4. Salbutamol, Ipratropium/ Salbutamol, Fluticasone, Montelukast	13	1053.64 ± 00.00	13 697.32	4. Salbutamol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	24	1480.67 ± 215.59	3 5536.11
5. Fenoterol/ Ipratropium, Fenoterol/ Ipratropium, Fluticasone, Theophylline	12	1138.44 ± 38.00	13 661.28	5. Theophylline, Fluticasone, Tiotropium, Salbutamol	22	1083.57 ± 218.15	2 3838.59
6. Prednisone, Fenoterol, Fluticasone, Theophylline	12	662.46 ± 58.70	7 949.62	6. Theophylline, Tiotropium, Budesonide/ Formoterol, Salbutamol	21	1104.32 ± 70.41	2 3190.77
7. Prednisone, Fluticasone, Montelukast, Theophylline	12	901.39 ± 166.23	10 816.73	7. Fenoterol/ Ipratropium, Tiotropium, Budesonide/ Formoterol, Theophylline	20	1153.62 ± 228.85	2 3072.46
8. Salbutamol/ Ipratropium, Formoterol, Prednisone, Salbutamol	12	463.26 ± 220.92	5 559.16	8. Ipratropium/ Salbutamol, Fluticasone, Tiotropium	20	1498.75 ± 351.92	2 9975.11
9. Prednisone, Fenoterol, Theophylline, Budesonide/ Formoterol	11	723.03 ± 24.62	7 953.42	9. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium	19	1252.45 ± 87.89	2 3796.62
10. Fenoterol/ Ipratropium, Fluticasone, Montelukast, Salbutamol	10	1049.29 ± 108.79	10 492.95	10. Salbutamol, Tiotropium, Budesonide/ Formoterol, Theophylline	19	1152.57 ± 84.77	2 1898.83

Table A13: The top 10 observations with four active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 335			2011 Products	Asthma & COPD = 116		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Ciclesonide, Prednisone, Salmeterol, Salbutamol	19	777.66 ± 128.97	14 775.66	1. Tiotropium, Budesonide/ Formoterol, Theophylline, Salbutamol	15	1170.09 ± 49.44	17 551.44
2. Formoterol, Budesonide, Theophylline, Salbutamol	14	484.47 ± 9.29	6 782.68	2. Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	14	1473.77 ± 125.29	20 632.81
3. Prednisone, Fenoterol, Theophylline, Budesonide/ Formoterol	14	744.91 ± 00.00	10 428.74	3. Salbutamol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	12	1684.12 ± 81.51	20 209.44
4. Budesonide, Theophylline, Salmeterol, Salbutamol	12	765.22 ± 30.24	9 182.66	4. Salbutamol/ Ipratropium, Fenoterol,/ Ipratropium, Fluticasone, Tiotropium	11	1724.19 ± 170.76	18 966.1
5. Fenoterol, Budesonide, Budesonide/ Formoterol, Theophylline	12	1032.69 ± 00.00	12 392.28	5. Fluticasone, Tiotropium, Theophylline, Salbutamol	8	1112.48 ± 261.73	8 899.84
6. Theophylline, Fluticasone, Montelukast, Salbutamol	11	871.83 ± 00.00	9 590.13	6. Fenoterol, Theophylline, Fluticasone, Tiotropium	6	1154.62 ± 121.37	6 927.77
7. Budesonide, Formoterol, Prednisone, Salbutamol	9	472.13 ± 52.76	4 249.2	7. Fenoterol/ Ipratropium, Formoterol, Fluticasone, Tiotropium	6	1111.25 ± 231.95	6 667.51
8. Salbutamol, Budesonide, Formoterol, Theophylline	9	491.52 ± 9.83	4 423.68	8. Salbutamol/ Ipratropium, Salmeterol/ Fluticasone, Theophylline, Salbutamol	5	913.34 ± 56.62	4 566.74
9. Ciclesonide, Formoterol, Montelukast, Salbutamol	8	969.93 ± 00.00	7 759.44	9. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium	4	1621.73 ± 420.92	6 486.93
10. Salbutamol, Budesonide, Formoterol, Ipratropium	8	562.56 ± 25.22	4 500.52	10. Salbutamol, Fenoterol/ Ipratropium, Salmeterol/ Fluticasone, Theophylline	4	566.94 ± 00.00	2 267.76

FIVE PRODUCTS:

Table A17: The top 10 observations with five active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 248			2008 Products	Asthma & COPD = 21		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Beclomethasone, Fenoterol, Budesonide, Theophylline, Budesonide/ Formoterol	12	807.51 ± 29.08	9 690.16	1. Salbutamol, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Salbutamol	6	845.94 ± 0.77	5 075.66
2. Fenoterol, Budesonide, Formoterol, Montelukast, Theophylline	9	949.158 ± 54.85	8 542.43	2. Bromhexine/ Orciprenaline, Fenoterol/ Ipratropium, Salbutamol/ Ipratropium, Formoterol, Theophylline, Fluticasone	5	1070.04 ± 99.25	5 350.24
3. Prednisone, Fenoterol, Montelukast, Budesonide/ Formoterol, Theophylline	8	858.24 ± 33.18	6 865.92	3. Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Formoterol, Theophylline, Salbutamol	4	1101.26 ± 293.30	4 405.07
4. Fenoterol/ Ipratropium, Formoterol, Prednisone, Tiotropium, Theophylline	6	995.25 ± 86.74	5 971.54	4. Fenoterol/ Ipratropium, Salbutamol, Fenoterol/ Ipratropium, Formoterol, Theophylline	1	444.76 ± 00.00	444.76
5. Salbutamol, Budesonide, Budesonide, Beclomethasone, Fluticasone	5	891.50 ± 18.88	4 457.51	5. Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Salbutamol/ Ipratropium	1	882.88 ± 00.00	882.88
6. Prednisone, Formoterol, Ipratropium, Theophylline, Budesonide/ Formoterol	4	695.89 ± 00.00	2 783.56	6. Ipratropium/ Salbutamol, Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Theophylline, Fluticasone	1	1736.21 ± 00.00	1 736.21
7. Prednisone isone, Fluticasone, Ipratropium, Theophylline, Salbutamol	4	1257.32 ± 00.00	5 029.28	7. Salmeterol, Theophylline, Salbutamol, Bromhexine/ Orciprenaline, Fenoterol/ Ipratropium	1	409.23 ± 00.00	409.23
8. Salbutamol, Fluticasone, Montelukast, Budesonide/ Formoterol, Salbutamol	4	1091 ± 21.90	4 364.00	8. Theophylline, Budesonide/ Formoterol, Salbutamol, Salbutamol, Salbutamol	1	578.09 ± 00.00	578.09
9. Zafirlukast, Fenoterol, Ipratropium, Fluticasone, Theophylline	4	1069.59 ± 00.00	4 278.36	9. Theophylline, Salmeterol, Budesonide/ Formoterol, Theophylline, Salbutamol	1	864.26 ± 00.00	864.26
10. Budesonide, Salmeterol, Montelukast, Theophylline, Salbutamol	3	912.12 ± 116.66	2 736.38				

Table A18: The top 10 observations with five active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 141			2009 Products	Asthma & COPD = 107		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Theophylline, Fluticasone, Salmeterol, Montelukast, Salbutamol	12	1098.37 ± 181.40	13 180.47	1. Fenoterol/ Ipratropium, Formoterol, Fluticasone, Tiotropium, Theophylline	11	1703.93 ± 519.88	18 743.26
2. Theophylline, Prednisone, Fluticasone, Tiotropium, Salbutamol	12	1080.35 ± 1130.64	12 964.25	2. Ipratropium/ Salbutamol, Tiotropium, Budesonide/ Formoterol Theophylline, Salbutamol,	11	1262.93 ± 86.50	13 892.24
3. Fenoterol/ Ipratropium, Prednisone, Montelukast, Budesonide/ Formoterol, Theophylline	5	1130.64 ± 00.00	5 653.2	3. Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	7	1453.13 ± 27.32	10 171.95
4. Zafirlukast, Fenoterol, Ipratropium, Fluticasone Theophylline, Salbutamol	5	1169.45 ± 00.00	5 847.25	4. Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	7	1917.2 ± 00.00	13 420.4
5. Ipratropium/ Salbutamol, Ipratropium, Fenoterol, Theophylline, Salbutamol	4	555.87 ± 48.95	2 223.48	5. Bromhexine/ Orciprenaline, Formoterol, Tiotropium, Theophylline, Salbutamol	5	1095.06 ± 2.11	5 475.33
6. Ipratropium/ Salbutamol, Theophylline, Prednisone, Fluticasone, Salbutamol	4	1306.80 ± 64.39	5 227.21	6. Salbutamol, Salbutamol/ Ipratropium, Formoterol, Theophylline, Tiotropium	5	1085.76 ± 00.00	5 428.80
7. Fenoterol/ Ipratropium, Prednisone, Theophylline, Fluticasone, Salbutamol	3	741.87 ± 179.73	2 225.61	7. Fenoterol/ Ipratropium, Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	4	1691.03 ± 00.00	6 764.12
8. Ipratropium, Salbutamol/ Ipratropium, Theophylline, Prednisone, Fluticasone	3	1378.45 ± 85.54	4 135.36	8. Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Salbutamol	4	1413.20 ± 267.96	5 652.83
9. Salbutamol/ Ipratropium Theophylline, Fluticasone, Montelukast, Tiotropium	3	1609.62 ± 209.26	4 828.86	9. Salbutamol, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Salbutamol	4	896.20 ± 45.03	3 584.81
10. Bromhexine/ Orciprenaline, Ipratropium/ Salbutamol, Methylprednisolone, Budesonide/ Formoterol Theophylline	2	906.62 ± 67.94	1 813.25	10. Salbutamol, Fenoterol, Fluticasone, Tiotropium, Theophylline	3	1414.33 ± 00.00	4 242.99

Table A19: The top 10 observations with five active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 157			2010 Products	Asthma & COPD = 71		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Ipratropium, Fluticasone, Montelukast, Theophylline, Salbutamol	11	1194.47 ± 50.96	13 139.25	**1. Fenoterol/ Ipratropium, Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline**	10	1676.07 ± 63.69	16 760.74
2. Salbutamol, Methylprednisolone, Montelukast, Tiotropium, Theophylline	8	1165.61 ± 6.82	9 324.92	**2. Fenoterol/ Ipratropium, Formoterol, Fluticasone, Tiotropium, Theophylline**	9	1407.61 ± 211.00	12 668.57
3. Theophylline, Prednisone, Fluticasone, Tiotropium, Salbutamol	8	1114.06 ± 157.93	8 912.52	**3. Ipratropium/ Salbutamol, Tiotropium, Budesonide/ Formoterol, Theophylline, Salbutamol**	7	1315.79 ± 52.94	9 210.55
4. Prednisone, Theophylline, Budesonide/ Formoterol, Salbutamol, Salbutamol	7	696.34 ± 29.69	4 874.38	**4. Salbutamol, Salbutamol/ Ipratropium, Fluticasone, Tiotropium, Theophylline**	5	1432.66 ± 17.71	7 163.33
5. Prednisone, Fenoterol/ Ipratropium, Montelukast, Budesonide/ Formoterol, Theophylline	5	1261.23 ± 262.85	6 306.16	**5. Bromhexine/ Orciprenaline, Ipratropium/ Salbutamol, Ipratropium/ Salbutamol, Salmeterol, Theophylline**	4	1163.67 ± 00.00	4 654.68
6. Salbutamol, Salmeterol, Montelukast, Budesonide/ Formoterol, Theophylline	5	1416.01 ± 38.49	7 080.05	**6. Salbutamol, Ipratropium/ Salbutamol, Formoterol, Theophylline, Tiotropium**	4	1085.76 ± 00.00	4 343.04
7. Formoterol, Theophylline, Montelukast, Budesonide/ Formoterol, Salbutamol	4	1294.14 ± 404.81	5 176.59	**7. Salbutamol/ Ipratropium, Theophylline, Tiotropium, Budesonide/ Formoterol, Salbutamol**	4	1481.86 ± 9.67	5 927.46
8. Salbutamol, Prednisone, Theophylline, Fluticasone, Montelukast	4	521.85 ± 549.95	2 087.40	**8. Fenoterol, Fenoterol/ Ipratropium, Tiotropium, Budesonide/ Formoterol, Theophylline**	2	1653.35 ± 00.00	3 306.70
9. Theophylline, Prednisone, Montelukast, Budesonide/ Formoterol Salbutamol	4	1094.74 ± 00.00	4 378.96	**9. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium, Salbutamol**	2	1114.4 0 ± 00.00	2 228.80
10. Fenoterol/ Ipratropium, Formoterol, Tiotropium, Montelukast, Theophylline	3	1228.24 ± 30.39	3 684.74	**10. Ipratropium/ Salbutamol, Theophylline, Fenoterol, Fluticasone, Tiotropium**	2	1913.2 ± 00.00	3 826.40

Table A20: The top 10 observations with five active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 3218			2011 Products	Asthma & COPD = 18		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Prednisone, Beclomethasone, Formoterol, Theophylline, Salbutamol	6	408.8 ± 00.00	2452.8	1. Fenoterol/ Ipratropium, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropuim	6	1 686.23 ± 00.00	10 117.38
2. Salmeterol/ Fluticasone, Ipratropium, Montelukast, Theophylline, Salbutamol	6	1 009.15 ± 14.61	6 054.93	2. Fenoterol/ Ipratropium, Fluticasone, Salmeterol, Tiotropium, Theophylline	5	1 679.14 ± 59.32	8 395.73
3. Budesonide, Formoterol, Theophylline, Montelukast, Salbutamol	4	1 073.78 ± 1.39	4 295.13	3. Fenoterol/ Ipratropium, Fenoterol/ Ipratropium, Fluticasone, Tiotropium, Theophylline	2	1 700.36 ± 00.00	3 400.72
4. Formoterol, Formoterol, Budesonide, Montelukast, Salbutamol	4	1 039.61 ± 47.30	4 158.44	4. Ipratropium/ Salbutamol, Budesonide/ Formoterol, Fenoterol/ Ipratropium, Salmeterol/ Fluticasone, Theophylline	1	1 254.32 ± 00.00	1 254.32
5. Salbutamol, Budesonide, Formoterol, Theophylline, Montelukast	2	891.95 ± 00.00	1 783.9	5. Ipratropium/ Salbutamol, Budesonide/ Formoterol, Ipratropium/ Salbutamol, Budesonide/ Formoterol, Theophylline	1	1 353.02 ± 00.00	1 353.02
6. Salbutamol, Fenoterol/ Ipratropium, Methylprednisolone, Montelukast, Theophylline	2	852.7 ± 00.00	1 705.4	6. Salmeterol/ Fluticasone, Fluticasone, Theophylline, Salmeterol/ Fluticasone, Theophylline	1	1 496.61 ± 00.00	1 496.61
7. Theophylline, Prednisone, Montelukast, Budesonide/ Formoterol, Salbutamol	2	1 077.71 ± 12.04	2 155.43	7. Salbutamol/ Ipratropium, Fluticasone, Salmeterol, Tiotropium, Theophylline	1	1 801.69 ± 00.00	1 801.69
8. Budesonide, Formoterol, Prednisone, Theophylline, Salbutamol	1	302.29 ± 00.00	302.29	8. Theophylline, Tiotropium, Budesonide/ Formoterol, Theophylline, Salbutamol	1	1 262.19 ±	1 262.19
9. Budesonide, Ipratropium/ Salbutamol, Fluticasone, Montelukast, Salbutamol	1	1 087.57 ± 00.00	1087.57				
10. Fenoterol/ Ipratropium, Tiotropium, Montelukast, Budesonide/ Formoterol, Theophylline	1	1 546.42 ± 00.00	1 546.42				

SIX PRODUCTS:

Table A21: The top 10 observations with six active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 56			2008 Products	Asthma & COPD = 14		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Zafirlukast, Fenoterol, Fluticasone, Ipratropium, Fluticasone, Theophylline	13	1 463.73 ± 33.84	19 028.55	1. Fenoterol/ Ipratropium, Ipratropium, Theophylline, Fluticasone, Montelukast, Budesonide/ Formoterol	2	2018.22 ± 72.85	4 036.45
2. Betamethasone, Salbutamol/ Ipratropium, Fenoterol/ Ipratropium, Budesonide, Budesonide/ Formoterol, Theophylline	2	1 811.54 ± 00.00	3 623.08	2. Aminophylline, Betamethasone, Prednisone, Theophylline, Fluticasone, Salbutamol	1	795.72 ± 00.00	795.72
3. Fenoterol, Hydrocortisone, Prednisone, Theophylline, Montelukast, Budesonide/ Formoterol	2	1 011.76 ± 14.29	2 023.52	3. Bromhexine/ Orciprenaline, Prednisone, Theophylline, Montelukast, Budesonide/ Formoterol, Salbutamol	1	886.01 ± 00.00	886.01
4. Fenoterol, Ipratropium, Prednisolone, Fluticasone, Montelukast, Salbutamol	2	805.9 ± 00.00	1 611.80	4. Fenoterol, Prednisone, Ipratropium, Fluticasone, Montelukast, Salbutamol	1	805.9 ± 00.00	805.9
5. Ipratropium, Fenoterol/ Ipratropium, Formoterol, Prednisone, Tiotropium, Theophylline	2	1 260.00 ± 00.00	2 520.00	5. Ipratropium, Ipratropium, Fenoterol, Theophylline, Fluticasone, Salbutamol	1	992.05 ± 00.00	992.05
6. Salbutamol, Ipratropium, Salmeterol, Montelukast, Budesonide/ Formoterol, Theophylline	2	1 387.94 ± 00.00	2 775.88	6. Ipratropium, Ipratropium/ Salbutamol, Theophylline, Prednisone, Fluticasone	1	1491.04 ± 00.00	1 491.04
7. Beclomethasone, Salbutamol/ Ipratropium, Formoterol, Budesonide, Prednisone, Salbutamol	1	1 048.45 ± 00.00	1 048.45	7. Ipratropium/ Salbutamol, Theophylline, Prednisone, Theophylline, Fluticasone, Salbutamol	1	1387.77 ± 00.00	1 387.77
8. Bromhexine/ Orciprenaline, Ipratropium/ Salbutamol, Budesonide, Methylprednisolone, Salmeterol, Theophylline	1	995.11 ± 00.00	995.11	8. Prednisone, Budesonide/ Formoterol, Prednisone, Budesonide/ Formoterol, Prednisone, Budesonide/ Formoterol	1	1225.57 ± 00.00	1 225.57
9. Bromhexine/ Orciprenaline, Methylprednisone, Beclomethasone, Theophylline, Salmeterol, Salbutamol	1	722.67 ± 00.00	722.67	9. Prednisone, Theophylline, Theophylline, Fenoterol/ Ipratropium, Prednisone, Theophylline	1	766.61 ± 00.00	766.61
10. Bromhexine/ Orciprenaline, Prednisone,	1	1 750.53 ± 00.00	175.53	10. Salbutamol, Fluticasone, Montelukast,	1	1740.54 ±	1 740.54

2008 Products	Asthma = 56			2008 Products	Asthma & COPD = 14		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
Theophylline, Bromhexine/ Orciprenaline, Prednisone, Theophylline				**Salbutamol, Fluticasone, Montelukast**		00.00	

Table A22: The top 10 observations with six active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 14			2009 Products	Asthma & COPD = 10		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fenoterol/ Ipratropium, Ipratropium, Theophylline, Fluticasone, Montelukast, Budesonide/ Formoterol	2	2 018.22 ± 72.58	4 036.45	1. Bromhexine/ Orciprenaline, Salbutamol/ Ipratropium, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium	5	1 498.36 ± 52.42	7 491.82
2. Aminophylline, Betamethasone, Prednisone, Theophylline, Fluticasone, Salbutamol	1	795.72 ± 00.00	795.72	2. Ipratropium/ Salbutamol, Tiotropium, Budesonide/ Formoterol, Theophylline, Theophylline, Salbutamol	1	1 456.59 ± 00.00	1 456.59
3. Bromhexine/ Orciprenaline, Prednisone, Theophylline, Montelukast, Budesonide/ Formoterol, Salbutamol	1	886.01 ± 00.00	886.01	3. Salbutamol, Fenoterol, Fluticasone, Tiotropium, Theophylline, Theophylline	1	1 367.83 ± 00.00	1 367.83
4. Fenoterol, Prednisolone, Ipratropium, Fluticasone, Montelukast, Salbutamol	1	805.9 ± 00.00	805.9	4. Salbutamol, Fenoterol, Salbutamol/ Ipratropium, Fluticasone, Tiotropium, Budesonide/ Formoterol	1	1 494.98 ± 00.00	1 494.98
5. Ipratropium, Fenoterol, Theophylline, Prednisone, Fluticasone, Salbutamol	1	992.05 ± 00 00	992.05	5. Salbutamol, Ipratropium/ Salbutamol, Salbutamol/ Ipratropium, Theophylline, Tiotropium, Budesonide/ Formoterol	1	1 522.43 ± 00.00	1 522.43
6. Ipratropium, Ipratropium/ Salbutamol, Theophylline, Prednisone, Fluticasone, Salbutamol	1	1 491.04 ± 00.00	1 491.04	6. Salbutamol/ Ipratropium, Theophylline, Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Theophylline, Tiotropium	1	1 105.35 ± 00.00	1 105.35
7. Ipratropium/ Salbutamol, Theophylline, Prednisone, Theophylline, Fluticasone, Salbutamol	1	1 387.77 ± 00.00	1 387.77				
8. Prednisone, Budesonide/ Formoterol, Prednisone, Budesonide/ Formoterol, Prednisone, Budesonide/ Formoterol	1	1 225.57 ± 00.00	1 225.57				
9. Prednisone, Theophylline, Theophylline, Fenoterol/ Ipratropium, Prednisone, Theophylline	1	766.61 ± 00.00	766.61				
10. Salbutamol, Fluticasone, Montelukast,	1	1 740.54 ± 00.00	4 036.45				

2009 Products	Asthma = 14			2009 Products	Asthma & COPD = 10		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
Salbutamol, Fluticasone, Montelukast							

Table A23: The top 10 observations with six active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 61			2010 Products	Asthma & COPD = 3		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Salbutamol, Ipratropium/ Salbutamol, Methylprednisone, Montelukast, Tiotropium, Theophylline	8	1 332.3 ± 00.00	10 658.4	**1. Fenoterol/ Ipratropium, Formoterol, Theophylline, Fenoterol/ Ipratropium, Formoterol, Theophylline**	1	1 108.84 ± 00.00	1 108.84
2. Theophylline, Prednisone, Montelukast, Tiotropium, Budesonide/ Formoterol, Salbutamol	6	1 415.98 ± 39.08	8 495.88	**2. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium, Theophylline, Salbutamol**	1	1 393.15 ± 00.00	1 393.15
3. Bromhexine/ Orciprenaline, Ipratropium/ Salbutamol, Salbutamol/ Ipratropium, Salmeterol, Montelukast, Theophylline	4	1 554.91 ± 00.00	6 219.64	**3. Tiotropium, Budesonide/ Formoterol, Theophylline, Salbutamol, Tiotropium, Salbutamol**	1	1 407.16 ± 00.00	1 407.16
4. Salbutamol, Prednisone, Ipratropium/ Salbutamol, Fluticasone, Montelukast, Budesonide/ Formoterol	4	1 577.63 ± 46.84	6 310.52				
5. Formoterol, Prednisone, Theophylline, Montelukast, Budesonide/ Formoterol, Salbutamol	3	1 185.39 ± 36.09	3 556.17				
6. Ipratropium, Fenoterol, Salbutamol/ Ipratropium, Montelukast, Budesonide/ Formoterol, Salbutamol	3	1 014.26 ± 00.00	3 042.78				
7. Salbutamol, Fenoterol/ Ipratropium, Tiotropium, Budesonide/ Formoterol, Theophylline	3	1 539.78 ± 18.90	4 619.36				
8. Ipratropium, Fenoterol/ Ipratropium, Fluticasone, Montelukast, Theophylline Salbutamol	2	1 429.63 ± 55.46	2 859.26				
9. Ipratropium, Formoterol, Theophylline, Prednisone, Theophylline, Fluticasone, Montelukast	2	1 326.18 ± 49.87	2 652.36				
10. Salbutamol, Ipratropium, Prednisone, Theophylline, Fluticasone, Montelukast	2	763.92 ± 620.04	1 527.84				

Table A24: The top 10 observations with six active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 3			2011 Products	Asthma & COPD = 7		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Salbutamol, Fenoterol/ Ipratropium, Tiotropium, Montelukast, Budesonide/ Formoterol, Theophylline	2	1 514.73 ± 00.00	3 029.46	1. Fenoterol/ Ipratropium, Fenoterol/ Ipratropium, Fluticasone, Salmeterol, Tiotropium, Theophylline	3	2 196.06 ± 63.98	6 588.20
2. Ciclesonide, Salmeterol, Montelukast, Ciclesonide, Salmeterol, Montelukast	1	2 469.26 ± 00.00	2 469.26	2. Salbutamol/ Ipratropium, Fenoterol/ Ipratropium, Fluticasone, Salmeterol, Tiotropium, Theophylline	2	2003.68 ± 13.54	4 007.37
				3. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium, Fenoterol/ Ipratropium, Salmeterol/ Fluticasone	1	2 708.74 ± 00.00	2 708.74
				4. Salbutamol/ Ipratropium, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium, Theophylline	1	1 721.57 ±	1 721.57

SEVEN PRODUCTS:

Table A25: The top 10 observations with seven active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 11			2008 Products	Asthma & COPD = 1		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Ipratropium, Fenoterol, Fluticasone, Prednisone, Budesonide, Montelukast, Salbutamol	3	1 068.46 ± 00.00	3 205.38	**1. Salbutamol, Fenoterol/ Ipratropium, Formoterol, Salbutamol, Fenoterol/ Ipratropium, Formoterol, Theophylline**	1	618.20 ± 00.00	618.20
2. Fenoterol/ Ipratropium, Budesonide, Theophylline, Bromhexine/ Orciprenaline, Fenoterol/ Ipratropium, Budesonide, Theophylline	1	878.51 ± 00.00	878.51				
3. Fenoterol/ Ipratropium, Fenoterol, Ipratropium/ Salbutamol, Budesonide, Prednisone, Budesonide, Theophylline	1	1 389.00 ± 00.00	1 389.00				
4. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Budesonide, Fluticasone, Salmeterol, Montelukast	1	1 684.43 ± 00.00	1 684.43				
5. Fluticasone, Montelukast, Theophylline, Fluticasone, Salmeterol, Montelukast, Salbutamol	1	1 700.87 ± 00.00	1 700.87				
6. Montelukast, Tiotropium, Theophylline, Fluticasone, Montelukast, Tiotropium, Theophylline	1	2 688.12 ± 00.00	2 688.12				
7. Salbutamol, Ipratropium, Prednisone, Salmeterol, Montelukast, Budesonide/ Formoterol, Theophylline	1	1 513.54 ± 00.00	1 513.54				
8. Salbutamol, Prednisone, Budesonide, Theophylline, Aminophylline, Betamethasone, Salbutamol	1	435.13 ± 00.00	435.13				
9. Theophylline/ Ethophylli, Salbutamol, Prednisone, Prednisone, Fluticasone,	1	1 114.36 ± 00.00	1 114.36				

2008 Products	Asthma = 11			2008 Products	Asthma & COPD = 1		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
Tiotropium, Theophylline							

Table A26: The top 10 observations with seven active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 3			2009 Products	Asthma & COPD = 1		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fluticasone, Tiotropium, Theophylline, Salbutamol, Fenoterol/Ipratropium, Fluticasone, Theophylline	1	1 876.84 ± 00.00	1 876.84	**1. Fluticasone, Tiotropium, Theophylline, Salbutamol, Fenoterol/ Ipratropium, Fluticasone, Theophylline**	1	1 876.84 ± 00.00	1 876.84
2. Ipratropium, Bromhexine/ Orciprenaline, Ipratropium/ Salbutamol, Prednisone, Theophylline, Montelukast, Budesonide/ Formoterol	1	1 161.69 ± 00.00	1 161.69				
3. Prednisone, Fenoterol/ Ipratropium, Budesonide/ Formoterol, Theophylline, Prednisone, Fenoterol/ Ipratropium, Theophylline	1	1 257.27 ± 00.00	1 257.27				

Table A27: The top 10 observations with seven active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 2			2010 products	Asthma & COPD = 1		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Bromhexine/ Orciprenaline, Betamethasone, Theophylline, Prednisone, Budesonide/ Formoterol, Salbutamol, Salbutamol	1	787.03 ± 00.00	787.03	**1. Fenoterol/ Ipratropium, Theophylline, Fluticasone, Tiotropium, Fenoterol/ Ipratropium, Salmeterol/ Fluticasone, Theophylline**	1	2 759.63 ± 00.00	2 759.63
2. Prednisone, Ipratropium, Ipratropium, Prednisone, Theophylline, Fluticasone, Salbutamol	1	1 028.67 ± 00.00	1 028.67				

Table A28: The top 10 observations with seven active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 1			2011 Products	Asthma & COPD = 0		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Salbutamol, Budesonide, Fenoterol/ Ipratropium, Tiotropium, Montelukast, Budesonide/ Formoterol, Theophylline	1	1 852.54 ± 00.00	1 852.54				

EIGHT PRODUCTS:

Table A29: The top 10 observations with eight active ingredients according to asthma and asthma/COPD prescriptions for 2008

2008 Products	Asthma = 1			2008 Products	Asthma & COPD = 1		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Budesonide, Fluticasone, Salmeterol, Montelukast	1	2 064.61 ± 00.00	2 064.61	**1. Ipratropium/ Salbutamol, Fenoterol/ Ipratropium, Theophylline, Fluticasone, Budesonide, Fluticasone, Salmeterol, Montelukast**	1	2 064.61 ± 00.00	2 064.61

Table A30: The top 10 observations with eight active ingredients according to asthma and asthma/COPD prescriptions for 2009

2009 Products	Asthma = 1			2009 Products	Asthma & COPD = 1		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
• **Fenoterol/ Ipratropium, Budesonide/ Formoterol, Salbutamol, Fenoterol/ Ipratropium, prednisone, Budesonide/ Formoterol, Montelukast, Salbutamol**	1	1 274.17 ± 00.00	1 274.17	**1. Fenoterol/ Ipratropium, Budesonide/ Formoterol, Salbutamol, Fenoterol/ Ipratropium, prednisone, Budesonide/ Formoterol, Montelukast, Salbutamol**	1	1 274.17 ± 00.00	1 274.17

Table A31: The top 10 observations with eight active ingredients according to asthma and asthma/COPD prescriptions for 2010

2010 Products	Asthma = 1			2010 Products	Asthma & COPD = 0		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fenoterol/ Ipratropium, Budesonide/ Formoterol, Salbutamol, Fenoterol/ Ipratropium, prednisone, Budesonide/ Formoterol, Montelukast, Salbutamol	1	1 274.17 ± 00.00	1 274.17				

Table A32: The top 10 observations with eight active ingredients according to asthma and asthma/COPD prescriptions for 2011

2011 Products	Asthma = 1			2011 Products	Asthma & COPD = 0		
	Frequency	Average cost (R)	Total cost (R)		Frequency	Average cost (R)	Total cost (R)
1. Fenoterol/ Ipratropium, Budesonide/ Formoterol, Salbutamol, Fenoterol/ Ipratropium, prednisone, Budesonide/ Formoterol, Montelukast, Salbutamol	1	1 274.17 ± 00.00	1274.17				

Apendix B

Table of disease according to their ICD-10 coding by the Council of Medical Schemes (CMS, 2013b)

Chronic Disease List	ICD-10 Code	Description of disease
Addison's Disease	E27.1	Primary adrenocortical insufficiency
	E45.8	Disorder of adrenal glan, unspecified
Asthma	J45	Asthma
	J45.8	Mixed Asthma
Bronchectasis	J47	Bronchietsis
	Q33.4	Congenital bronchectasis
Cardiac Failure	I50	Heart Failure
	I50.0	Conggestive heart failure
	I50.1	Left ventricular failure
Cardiomyopathy	I42	Cardiomyopathy
	I42.0	Dilated cardiomyopathy
	I25.5	Iscaemic cardiomyopathy
Chronic Renal Disease	N03	Chronic nephritic syndrome
	N11	Chronoic tubule – interstitial nephritis
	N18	Chronic renal failure
COPD	J43	Emphysema
	J44	Other chronics obstructive pulmonary disease
Coronary Artery Disease	I20	Angina pectoris
	I20.0	Unstable angina
	I22	Chronic ischeamic heart disease
Crohn's Disease	K50	Crohn's Disease (regional enteritis)
	K50.8	Other Crohn's Disease
Diabetes Inspidus	E23.2	Diabetes inspidus
Diabetes Mellitus Type 1	E11	Insulin-Dependent Diabetes Mellitus
	E11.6	Insulin-Dependent Diabetes Mellitus with other specified complications
	E11.9	Insulin-Dependent Diabetes Mellitus with complication
Diabetes Mellitus Type 2	E11	Non-Insulin-Dependent Diabetes Mellitus
	E11.6	Non-Insulin-Dependent Diabetes Mellitus with other specified complications

	E11.9	Non-Insulin-Dependent Diabetes Mellitus Mellitus with complication
Dysrhythmias	I49	Other cardiac arrhythmias
	I47.2	Ventricalur tachycardia
	I48	Atrial fibrillation and flutter
Epilepsy	G40	Epilepsy
	G40.8	Other Epilepsy
Glaucoma	H40	Glaucoma
	Q15.0	Congenital Glaucoma
Heamophillia	D66	Hereditary Factor VIII Deficiency
	D67	Hereditary Factor XI Deficiency
Hyperlipidaemia	E78.0	Pure Hypercholesterolaemia
	E78.2	Mixed Hyperliideamia
	E78.5	Hyperlipidaemia, Unspecified
Hypertension	I10	Essential (primary) hypertension
	I11	Hypertensive heart disease
	I15	Secondary hypertension
Hypothyriodism	E02	Subclinical iodine-deficiency Hypothyriodism
	E03	Other Hypothyriodism
	E03.8	Other specified Hypothyriodism
Multipale Sclerosis	G35	Multipale Sclerosis
Parkinson's Disease	G20	Parkinson's Disease
	G21	Secondary Parkinsonism
Rheamatoid Arthritis	M05	Seropositive Rheamatoid Arthritis
	M06	Other Rheamatoid Arthritis
	M08.0	Juvenile Rheamatoid Arthritis
Schizophrenia	F20	Schizophrenia
	F20.8	Other Schizophrenia
Systemic Lupus Erythematosus (SLE)	M32	Systemic Lupus Erythematosus
	L93	Lupus Erythematosus
	L93.2	Other local Lupus Erythematosus
Ulcerative Colitis	K51	Ulcerative Colitis
	K51.8	Other Ulcerative Colitis unspecified

Appendix C

Treatment algorithm of COPD adapted from the Council of medical Schemes (CMS, 2013b)